WHO/VSQ/97.01
ENGLISH ONLY
DISTR.: LIMITED

A WHO guide to good manufacturing practice (GMP) requirements

Part 1: Standard operating procedures and master formulae

Written by:

Gillian Chaloner-Larsson, Ph.D, GCL Bioconsult, Ottawa
Roger Anderson, Ph.D, Director of Quality Operations, Massachusetts Public Health Biologic Labs
Anik Egan, BSc.,GCL Bioconsult, Ottawa

In collaboration with:

Manoel Antonio da Fonseca Costa Filho, M.Sc., Consultant in Quality Assurance, Biomanguinhos/ FIOCRUZ, Brazil
Dr Jorge F. Gomez Herrera, Director of Quality Assurance, Gerencia General de Biologicos y Reactivos, Secretaria De Salud, Mexico

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
VACCINE SUPPLY AND QUALITY
GLOBAL TRAINING NETWORK

World Health Organization
Geneva
1997

The Global Training Network is designed for staff of National Control Authorities and selected vaccine manufacturers meeting specific entrance criteria. This document is designed for use by participants in the Global Training Network, specifically for those participating in curricula related to Good Manufacturing Practices.

Curricula and curricula material for the Global Training Network have been overseen by Expert Review Panels convened at the request of WHO and comprised of experts internationally known for their proficiency in the particular field. The Vaccine Supply and Quality Unit would like to particularly thank the experts who reviewed this document and served on the Expert Review Panel: Dr Ian Sykes, Pharmaceutical Consultancy Service, Haastrecht, Netherlands, Dr Chung K Lee, Salk Institute, Swiftwater, Pennsylvania, USA, and Ms Carolyn Woodruff, Therapeutic Goods Administration, Melbourne, Victoria, Australia. The Global Training Network is financed in part through funds donated by the World Bank.

The Vaccine Supply and Quality Unit of the Global Programme for Vaccines and Immunization thanks the following donors whose financial support has made the production of this document possible: the World Bank, USAID, JICA, the Rockefeller Foundation and the Governments of Australia, China, Republic of Korea, Denmark, Ireland, Japan, Netherlands, Norway, Sweden, and the United Kingdom of Great Britain and Northern Ireland.

Copies may be requested from:

World Health Organization
Global Programme for Vaccines and Immunization
CH-1211 Geneva 27, Switzerland

Telephone: +22 791 4373/4421 • *Fax:* +22 791 4193/4192 • *E-mail:* gpv@who.ch

Printed: January 1997

Contents

Abbreviations

EP:	European Pharmacopoeia
GMP:	Good Manufacturing Practices
MF:	Master Formulae
QA:	Quality Assurance
QC:	Quality Control
QO:	Quality Operations
SOP:	Standard Operating Procedure
TRS:	Technical Report Series (publication of the World Health Organization)
USP:	United States Pharmacopoeia
WHO:	World Health Organization

1. Introduction and purpose of the guide

This guidance document has been prepared to provide a framework to aid vaccine manufacturers to assess their planned or existing documents describing the methods used to produce and test, and administratively control the manufacture of a vaccine. The framework is based on the World Health Organization (WHO) requirements for Good Manufacturing Practices (GMP), but in addition, other GMP Regulations/Guidelines and publications were consulted during preparation of the Guide. These references are listed in Appendix 3. The terms used, including the glossary (Appendix 4), and the overall direction of this guide follows the WHO GMP requirements.

The Guide provides a summary of the range of "written procedures" which are identified in the WHO's documents on GMP (ref. 21, 27), a presentation of a format for a Standard Operating Procedure (SOP) and accompanying data recording form, several sample SOPs, and summaries of the expected contents of several types of SOPs. It also provides information on the preparation of Master Formulae and batch processing records which are the written instructions and recording form for the production and control process.

In addition to the examples, the three vaccine manufacturers who collaborated in the preparation of this guide have contributed a full list of the titles of their SOPs, and copies of several SOPs from their facilities. These lists and examples are presented to aid manufacturers in developing the full range of SOPs required with suitably detailed instructions for performance and recording data. Altogether, 24 SOPs have been presented in this Guide providing examples of the range of documents needed. These can be used by manufacturers as examples or reference for preparing or revising their own Standard Operating Procedures.

This guide for SOPs and Master Formulae is Part 1 of 2: Part 2 is a guide to Validation.

2. Good manufacturing practices (GMP)

WHO defines Good Manufacturing Practices (GMP) as "that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization" (ref 27). GMP covers all aspects of the manufacturing process: defined manufacturing process; validated critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved written procedures and instructions; records to show all steps of defined procedures taken; full traceability of a product through batch processing records and distribution records; and systems for recall and investigation of complaints.

The guiding principle of GMP is that quality is built into a product, and not just tested into a finished product. Therefore, the assurance is that the product not only meets the final specifications, but that it has been made by the same procedures under the same conditions each and every time it is made. There are many ways this is controlled - controlling the quality of the facility and its systems, controlling the quality of the starting materials, controlling the quality of production at all stages, controlling the quality of the testing of the product, controlling the identity of materials by adequate labelling and segregation, controlling the quality of materials and product by adequate storage, etc. All of these controls must follow prescribed, formal, approved procedures, written as protocols, SOPs, or Master Formulae, describing all the tasks carried out in an entire manufacturing and control process.

3. Quality management

Quality management in the drug industry is discussed in the WHO GMP for Pharmaceutical Products (ref 27). In this document the following are presented:

- The basic elements of quality management are:

  - an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes, and resources; and

  - systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance".

- The concepts of quality assurance, GMP, and quality control are interrelated aspects of quality management. They are of "fundamental importance to the production and control of pharmaceutical products".

QA encompasses all of the arrangements made to ensure that pharmaceutical products meet the quality required for their intended use. Although QA is not specified in all GMP documents, the WHO GMP guidelines (ref 27) present the principles of QA are to ensure that GMP and other regulatory codes (GLP - Good Laboratory Practice, and GCP - Good Clinical Practice) are respected; that responsibilities are clearly specified; all testing, controls, calibrations, validations, etc are performed as specified; that products are not sold before the correct authorizations have been obtained; that products are appropriately handled throughout their shelf-life; and that there is a procedure for self inspections (quality audit).

All GMP Regulations or Guidelines agree that the independence of quality control from production is fundamental. QC specifically involves sampling, determining specifications, and testing and approving of starting materials, intermediate and final product; maintaining records of all sampling, inspecting, testing; ensuring that deviations are recorded and investigated; retaining sufficient samples to permit future examination; and to ensure that no product is released without the certification required by the marketing authorization (product licence, registration certificate).

Depending on the size of a pharmaceutical manufacturer, the number of products manufactured, the complexity of the operations, and the requirements of the local regulatory authorities, the system of "quality management" will differ. A company can range from: i) a small single product facility with a production and QC department and a quality assurance programme which performs quality audits with a team comprised of staff from the two departments; to: ii) a large multi-product company with production, quality control, quality assurance, engineering, and regulatory affairs departments. Provided that the quality assurance system, incorporating GMP

and quality control, is well planned, with all functions specified and appropriately implemented, and the regulatory requirements taken into account, the allocation of specific duties to QA and QC may vary .

When writing SOPs, the section identifying the responsibilities for approvals or authorizations will reflect the quality management structure of the company. Each SOP example given in this guide presents one of many possibilities for assigning authorization responsibilities to QA and QC, and in several cases either QA or QC has been indicated.

4. Documentation

Documentation is the key to operating a pharmaceutical company in compliance with GMP requirements. The system of documentation devised or adopted should have as its main objective to establish, monitor, and record "quality" for all aspects of the production and quality control. Several types of documents are needed to accomplish this.

4.1 Standard operating procedures, specifications and master formulae

Descriptive documents give instructions on how to perform a procedure or a study, or give a description of specifications. The instruction type documents are: standard operating procedures (SOP); protocols (for validation studies, stability studies, safety studies); and master formulae (manufacturing instructions). Each of these gives instruction on how to perform specific procedures. Specifications describe the required characteristics or composition of a product or material or test. These kinds of documents provide the specific details defining the quality of incoming materials, the quality of the production environment, the quality of the production and control process, and the quality of the final product.

4.2 Forms for recording data

Another type of documentation is the form used for recording data as it is taken during the performance of tasks, tests, or events. These are forms (datasheets, or data record forms), reports, batch processing records, and equipment log books. These documents provide the evidence that the raw materials, facility environment, the production process, and the final product consistently meet the established quality requirements.

4.3 Identification numbers

There are also the identification systems or codes devised to number and track both information and documents. These are SOP numbers, equipment numbers, form numbers, receiving codes, and batch/lot numbers. These numbering systems should be designed so that procedures, processes and materials can be traced throughout the data records.

4.4 Labels

Labelling systems are used to identify the status of the equipment or facility, restricted areas, and warning labels. These include raw material tags, quarantine labels, release labels, reject labels, labels to identify specific storage areas, biohazard or radioactive labels, restricted access labels, equipment "cleaned" or "waiting for cleaning" labels, process intermediate labels, and the final product labels. These permit the identification and tracking of materials, of the progress of a production process, and assurance of the proper functioning of equipment.

The WHO guidelines for Good Manufacturing Practices (ref. 21, 27) and all other national and international GMP Guidelines and Regulations (ref. 3, 5, 7, 11, 18, 19) emphasize the requirement for complete documentation. A well-structured documentation system, including SOPs for the regular document review and revision, provides the structure for recording the evidence for the quality of the product.

All documentation must be organized into files which must be maintained for specified periods of time after the expiry date of the product.

A well-designed documentation system is useful only if it is well used. The system must include quality assurance procedures to ensure that instructions are followed, that labels and numbering systems are properly used and recorded, and that data record forms and batch processing records are assembled and reviewed. Control and assessment of the documentation system itself is a significant management tool that permits an ongoing assessment of the changes and revisions necessary to remain in compliance, to delete what is unnecessary or redundant and to improve procedures or processes.

5. Range of requirements for written procedures

Throughout the WHO GMP Guidelines, in addition to sections on document requirements, many references are made to the need for written procedures for specific aspects of the manufacturing process. There is a broad range of SOPs needed for a pharmaceutical manufacturing establishment. GMP Guidelines and Regulations for pharmaceuticals, sterile products, and biologicals from WHO, the EU and several other countries make reference to 'written procedures" throughout the documents. In Appendix 2 of this Guide, a list of the titles of the SOPs from three vaccine manufacturers is presented to give an idea of the SOPs needed by a manufacturer.

A review of WHO's GMP Requirements for reference to "written procedures" resulted in a long list of operations and activities which must follow written approved procedures. The list covered the requirements for all aspects of the control of quality: raw materials and packaging materials, the premises, the equipment, the test procedures, the production, personnel performance, and quality assurance.

Appendix 1 of this Guide lists a range of the types of procedures which should be prepared in written format. Others may be required depending on the products manufactured, on the size of operations, and on the management structure of the company.

6. Standard operating procedures (SOPs)

Standard operating procedures (SOPs) are the detailed written instructions that specify how a test or administrative procedure is to be performed, or how a piece of equipment is operated, maintained and calibrated. SOPs describe the "standard" approved procedures that are routinely carried out in a GMP facility. They indicate exactly how things are done, and are kept current by review and approved revision on a predetermined schedule (usually annual), or when planned changes are made to the procedure or equipment and reagents used in the procedure. The original of a current version of an SOPs is maintained in a central file, and copies are distributed to the locations where the procedure is performed. The procedure for describing the writing, revising and approving of SOPs and the control of distribution of SOPs is one of the important quality assurance procedures. The term “change control” has recently been introduced to the vocabulary of pharmaceutical manufacturing and control. Although this is primarily a term for validation procedures, it may also apply to the control of the review and revision of SOPs for routine procedures. Any SOP describing the distribution and control of documents must clearly indicate the mechanisms by which SOPs can be modified or changed: from assessment and rationale for the need for a change, to the evaluation of other SOPs that might be changed as a result, to the final approval of changes and the implementation of the changed procedure. SOPs are used as a reference by the persons responsible for the performance, and are also used for training new operators in the performance of the procedure. Quality assurance procedures should be in place to ensure that SOPs are enforced and properly used.

SOPs follow a scientific format, and are written with the view that they will be used by persons trained in the procedure. They should be specific instructions for each step in sequential order including the preparatory work which must be done before starting the main procedure, as well as instructions for recording and reporting the results. There is little need for excess text on theory and background - what is required is clear concise instructions for carrying out a procedure which has been approved.

Usually the initial draft of an SOP is written by the person performing the procedure or by someone who knows the procedure well and must be written including the details and the time course of the tasks. Supervisors review the SOPs for completeness and content and QC or QA staff approve for regulatory compliance.

When appropriate, a formal data sheet or data record form is prepared for an SOP. This form is a parallel summary document with checklists, checkboxes, and blanks for all data to be recorded during the performance of the procedure. It also has spaces for signatures of the operator and other technicians who verify and countersign certain critical operations during the procedure. Finally, there is the space for the signature of the department supervisor who reviewed the completed data record form. Such blanks

and checklists ensure that the required data are collected, that nothing is overlooked and also provide the evidence that the procedure was performed according to the SOP. The datasheets also provide instructions for recording deviations to the procedure, for calculations or reporting requirements, for comparison of results with predetermined specifications, and the criteria for repeating procedures in cases where unacceptable results were obtained.

7. Format for standard operating procedures (SOPs)

This section of the guide presents a basic format for an SOP with instructions on what information should be provided. It also gives information for the design of data record forms. Several specific SOPs have been presented in this format, and instructions and examples have been presented indicating the type of information which should be included for other types of SOPs.

The formats and sample SOPs can be used, modified, or redesigned by each manufacturer according to their organizational structure, and by the complexity of their manufacturing operations.

The information in the format is essentially an SOP describing "How to Write an SOP".

Format for a standard operating procedure (SOP)

Name of facility _____ **page ..... of .....**

SOP Number _____ Title _____

Revision number _____

Written by _____ Edited by _____

Authorization signature _____ Department _____ Date _____

Effective date _____ Replaces _____

Purpose:

WHY:

Why is this procedure written.

Why is it being performed.

Scope

WHEN:

Indicate when this procedure needs to be performed.

WHERE:

Indicate where this procedure applies.

Responsibility

WHO:

Who performs the procedure, who is responsible to see it is performed correctly.

Materials and equipment

WHAT: What is needed to perform the test. The list should be complete and specific.

SOP Number: ..... Rev.....Name of facility ..... page ..... of .....
Short title: .....

Procedure

HOW:

Clear concise, step by step instructions on how to perform the procedure. This should be written as instructions for the operator to follow, without a lot of theoretical background. A section on fundamental principles can be included if necessary.

It should include:

a) Preliminary steps that must be done before beginning the actual procedure.

b) Safety considerations: Precautions for work with physical, chemical, or biological hazards (cotainment facility clothing, masks, hoods, goggles, gloves, cleanup of spills etc.).

c) The chronological instructions. It is useful to number the steps so that repeat steps can be referred to rather than making the SOP very long.

d) Calculations: Explanations and sample of how to do any required calculations.

Reporting

WHAT NEXT:

a) Indicate where the results should be recorded.

b) Explain what to do if there are problems during the test.

c) Indicate that deviations to the procedure must be approved and recorded.

d) Identify the person to whom the final results should be reported.

Reference documents:

List other SOPs which directly affect or are relevant to this procedure. For example, the SOP for making a buffer used in the procedure, or the SOP for the operation of a piece of equipment used in the procedure.

8. Forms for recording data

Forms for recording the data generated during the performance of a procedure are especially important for analytical assays (either in-process tests or quality control release tests) and are appropriate for many other procedures as well (equipment calibration, environmental monitoring, cleaning procedures, etc). Such data record forms (also called datasheets, worksheets, data collection forms) can be appendices to the SOP, or separately numbered documents, but are recommended as a most appropriate way to ensure that the required data is taken. (Laboratory notebooks where data are entered informally on blank pages with no specified data fields are not considered appropriate for GMP operations).

These data record forms are completed by the technician while performing a procedure described in an SOP. The forms include brief instructions which correspond to the SOP. The forms are designed to record all the data required for a specific SOP in the order that data are to be taken. The forms include blanks for the required raw data, dates, times, identification of equipment, identification of technicians, and places for signatures or initials where appropriate. The technicians enter the raw data as they carry out the procedure and fill in blanks, tick off on checklists, or checking off of checklists, or circle appropriate answers. The datasheets should be designed to keep writing to a minimum. Checklists are appropriate for equipment and materials preparation; blanks are suitable for lot numbers, dates, times, temperatures, identification numbers, room numbers, fridge or freezer numbers, calibration values, raw data readings, calculations; circling answers can be used for Y/N or Pass/Fail, or for choosing among options, etc.

Each form should have the name of the company, the title, the number and revision number of the form (or of the SOP if it is an appendix), the number of the SOP, page numbers, and signature and date blanks for the operator (technician) and for the verification signature (for accuracy, completeness, and compliance). The data to be collected are specifically described and approved in the SOP. There should be instructions for the correction of data: mistakes made during data entry must be crossed out and the correct value entered and initialled. There must be no erasures or use of "white out".

Once completed, and verified by a supervisor, the completed form is approved, filed and/or distributed according to the instructions in the SOP (e.g. data to authorized person or department for approval). The original should be kept in a secure location, and a copy should go to the batch processing record file.

Format for a data record form

Data Record Form #..... rev #..... Name of facility.....page..... of .....
SOP reference number.....

Title _____

Preparation

Materials checklist (buffers, glassware, supplies, QC approved dates if required)

Equipment checklist (including specific numbers if there is a choice)

Buffer, media, cleaning solution, etc preparation if necessary. Reference to SOP

Step by step Instructions

Presented in the order in which the work is routinely performed.

Brief instructions with blanks for all data to be filled in.

Dates and times for all operations, especially if procedure takes several days, or if there are specification limits to be met.

Blank for verification signature for critical steps where necessary.

Blanks for calculations as required and in order performed.

Instructions for sending intermediate samples for testing, if appropriate.

Instructions for storage during any waiting periods.

Criteria for repeating test or procedure.

Instructions for reporting any deviations, or problems.

Instructions for correcting mistakes (no erasures, cross-out, add correct information and initials)

Signatures

Operator (technician) _____ Date _____

Verification (supervisor)_____ Date _____

Instructions for filing and approval

State where completed data sheet is to be delivered, copied, and filed.

Submit to QC or QA for review and approval of the data.

9. Example SOPs

Several SOPs have been prepared in the format proposed for SOPs (some include forms for recording data) and other examples provide the content requirements for preparing SOPs for several other procedures.

9.1 Samples of SOPs prepared in the proposed format.

SOP # ABC-1 Operation, Maintenance and Calibration of Incubator Model Number zzz, from Supplier XXX.

SOP # ABC-2 Batch Processing Record Review

SOP # ABC-3 Determination of Lf/mL for Tetanus by the Ramon Titration Method.

SOP # ABC-4 Reporting of Production Incidents/Deviations and Resulting Actions.

SOP # ABC-5 Responsibilities of Quality Operations (QO) Departments.

SOP # ABC-6 Quality Audits, General

SOP # ABC-7 Method for Sampling Raw Materials and Production Components

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *3*

SOP Number *ABC-1*

Title *Operation, Maintenance and Calibration of Incubator Model Number zzz, from Supplier XXX*

Revision number *2*

Written by _____ Edited by _____

Authorization signature _____ Department (QA/QC) _____ Date _____

Effective date *Aug 21, 1994* Replaces: *Revision 1 dated: Jan 2, 1992*

1. Purpose

This procedure explains the operation, maintenance and calibration of Supplier XXX, Incubator Model Number zzz.

2. Scope

This SOP is for the incubator located in the QC microbiology laboratory. It will be used to incubate samples for growth of microorganisms such as media; environmental control samples; water test samples; api identification samples; and for other microbiological tests. This incubator must not be used for any other purposes than those indicated.

3. Responsibility

3.1 The QC microbiologist is responsible for the correct operation, routine maintenance or setting, and cleaning and disinfecting of the incubator, and recording all operations in the incubator log. The QC lab manager is responsible for ensuring these procedures are followed.

3.2 The Maintenance department is responsible for making adjustments and repairs to the incubator and for recording them in the maintenance log.

3.3 QA must be notified of any repairs via an incident/deviation report.

3.4 QA is responsible for performing the yearly calibrations and for assessing the need for revalidation after repairs.

4. Materials and Equipment

4.1 Incubator, Supplier XXX, model zzz, serial no. 000-000

Description: Temp range: +5 to 70 °C
Temp uniformity: ±0.25 @ 37°C
Chamber volume: 10 ft^3
Interior electric outlet
Safety over-temperature protection
Digital microprocessor control system

4.2 Thermometer (certified), model T, Manufacturer Z, range 0-80°C

4.3 Cleaning solutions: AA, BB

4.4 NIST (or other standard) -traceable reference thermometer zz

4.5 Maintenance log

5. Procedure

5.1 Operation

5.1.1 Turn on power.

5.1.2 Set temperature: press UP or DOWN on the arrow pad.

5.1.3 Let temperature stabilize for 60 minutes.

5.1.4 Set high limit thermostat (briefly summarize according to manual or refer to section inthe manual).

5.2 Temperature verification: Every day (the first activity when arriving at the laboratory)

5.2.1 Check the calibration date of the certified thermometer (to be recertified every 3-6 weeks)

5.2.2 Check the temperature on the digital readout and with the certified thermometer and record in the Incubator log book.

5.2.3 Notify supervisor and Engineering Department:

1) if digital readout and thermometer temperatures differ by > 0.5°C

2) if thermometer is outside the accepted range specified on the incubator

5.3 Maintenance: Monthly

5.3.1 Prepare a solution of the cleaning reagent (rotate cleaning agent each month)

5.3.2 Wash interior surfaces and shelves.

5.4 Calibration: Once a year QA will calibrate the incubator at three different temperatures (eg 25°C, 35°C, 45°C)

5.4.1 Set the first calibration temperature as in step 5.1.2

5.4.2 Place the reference thermometer in the center of the incubator ensuring the bulb does not touch the shelves.

5.4.3 Wait 60 minutes for the incubator temperature to stabilize.

5.4.4 Compare the reading on the reference thermometer with the digital display.

5.4.5 If there is a difference:

5.4.5.1 Put the display into calibration mode by pressing on up and down arrows simultaneously for 5 seconds until decimal points are flashing.

5.4.5.2 Press up or down arrows to change temperature setting to match the reference temperature and the certified thermometer.

5.4.5.3 Allow the incubator temperature to stabilize and repeat step 5.4.4 and if necessary step 5.4.5.

5.4.6 Repeat section 5.4.1 to 5.4.5 for two other temperatures.

6. Reporting

6.1 Record each use in the incubator log (date, time, temperature, high limit, operator, samples, date out)

6.1.1 All samples in the incubator must be clearly marked.

6.2 Record maintenance information and calibration data in the log (date, time, cleaning solution, operator).

6.3 Record all calibration data in the incubator log (date time, set temperatures, digital temperature, thermometer temperature, operator)

6.4 Report all problems in the operation of the incubator immediately to the supervisor.

6.5 Update calibration sticker.

7. Reference Documents

SOP:___ Preparation and Testing of Cleaning Solutions

XXX Incubator Manual for model zzz.

SOP:___ Thermometer Certification Method for Model T, Manufacturer Z, range 0-80°C

INCUBATOR LOG

Incubator # _____ Location: _____

Samples entered					
Date/Time (yr/mo/d/hr)	**Samples entered**	**Temperature (High limit)**	**Operator initials**	**Date out (yr/mo/d/hr)**	**Operator initials**
		( )			
		( )			
		( )			
		( )			
		( )			

(01)

Data record form: *rrr* **Rev** 2 **Name of facility** *ABC Vaccine Manuf Co.* **page** *2* **of** *..2..*
SOP Number: *ABC-1*

INCUBATOR MAINTENANCE LOG (a logbook, or sections of a logbook ,for each of these maintenance records is needed)

Incubator # _____; Location: _____

Daily temperature		
Date / Time (yr/mo/d/hr)	**Daily temperature**	**Operator initials**

(02)

Routine maintenance -- monthly		
Date / Time (yr/mo/d/hr)	**Maintenance cleaning solution**	**Operator initials**

(03)

Annual calibration				
Date / Time (yr/mo/d/hr)	**Calibration thermometer**	**Digital readout**	**Adjusted temperature**	**Operator initials**
	1 2 3	1 2 3	1 2 3	
	1 2 3	1 2 3	1 2 3	
	1 2 3	1 2 3	1 2 3	

(04)

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *2*

SOP Number *ABC-2*

Title *Batch Processing Record Review*

Revision number *3*

Written by _____ Edited by _____

Authorization signature _____ Department (QA/QC) _____ Date _____

Effective date *March 21, 1994* Replaces: *Revision 2 dated: Jan 2, 1993 .*

1. Purpose

The purpose of this SOP is to describe the procedure of batch processing record review and approval. Batch processing records are reviewed to determine compliance with all the approved written procedures before a batch is released for the next stage of processing or for distribution.

2. Scope

This SOP applies to the Production Department and the Quality Control Department. It may also apply to some operations by the Research Department.

3. Responsibility

3.1 It is the responsibility of the Department Manager to review each batch processing record after the lot has been produced.

3.2 It is the responsibility of Quality Assurance to review every batch record for completeness and accuracy.

3.3 It is the responsibility of QA to review and update this SOP as required.

4. Materials and Equipment: Batch processing records.

5. Procedure

5.1 When the batch processing record has been assembled and reviewed by the Department, it is submitted to QA for review and approval

5.2 Review:

5.2.1 Accurate component lot numbers

5.2.2 Completed forms

All blanks filled in
All choices marked
All initials, signatures, and second signatures present
All data entered in ink

5.2.3 All dates agree

5.2.4 Corrections
Crossout of original with a single line, initialled and dated.

5. Procedure, continued

5.2 Review, continued

5.2.5 Calculations correct

5.2.6 Summary pages agree with in-process records

5.2.7 Autoclave data agrees with charts

5.2.8 Expiration dates for in-house solutions are accurate: components were not expired at the time of preparation.

5.2.9 Solutions are used before expiry date

5.2.10 All data meet criteria of acceptance

5.2.11 Deviations were recorded, dated and initialed by the operator and countersigned by the Department Manager.

5.2.12 All pages are in the Batch Processing Record.

5.3 Approval: Batches must be approved before release for distribution. Any unexplained discrepancy or failure of a batch, or any of its components, to meet any of the specifications must be investigated through an Incident/Deviation Report. If necessary, the investigations will extend to other batches of the same product which might be associated with the specific failure or discrepancy.

6. Reference Documents

SOP #_____: Reporting of Production Incidents/Deviations and Resulting Actions.

Master Production Record Form for product

Batch Record Summary Sheet for product.

Data record form: _xxx_ **Rev** _3_ **Name of facility** _ABC Vaccine Manuf Co._ **page** _1_ **of** _..1.._
SOP reference number: _ABC-2_

QA: Batch processintg records review and approval log						
Dept.	**Lot #**	**Date received**	**Received by**	**Date reviewed**	**Reviewed by**	**Comments**

(05)

Name of Facility *ABC Vaccine Manufacturing Co.* **page** *1* **of** *3*

SOP Number *ABC-3*

Title *Determination of Lf/mL for Tetanus by the Ramon Titration Method* .

Revision number *0*

Written by _____ Edited by _____

Authorization signature _____ Department (QA/QC) _____ Date _____

Effective date *May 12, 1993* Replaces *new*

1. Purpose

This SOP describes the Ramon titration method for determining the Lf/mL of tetanus.

2. Scope

This procedure is used to determine the Lf/ml of tetanus toxin, tetanus toxoid, or tetanus vaccine, adsorbed.

3. Responsibility

3.1 The production department technicians are responsible for performing in-process Lf tests, and the production supervisor is responsible for ensuring that this SOP is followed.

4. Materials and Equipment

Note: when performed for in-process tests in the clean room, the equipment, reagents and glassware must be prepared and approved for clean room use.

4.1 Chemicals and reagents

4.1.1 Saline solution (0.85% NaCl).

4.1.2 Reference antitoxin, equine. Commercial preparation meeting WHO standards diluted to 100 Lf/mL with 0.85% NaCl (aliquoted and stored at 4°C, and has not passed expiry date).

4.1.3 Standard tetanus vaccine. Commercial preparation meeting WHO specifications, and an in-house standard.

4.1.4 Sodium citrate (powder).

4.2 Equipment

4.2.1 Waterbath set at 45°C. Model WB

4.2.2 Lamp for observation of flocculation

4.2.3 Balance, model B.

4.2.4 Clock or stopwatch

4.2.5 Convex lens

4. Materials and Equipment, cont'd

4.3 Glassware and supplies

4.3.1 Pipettes, 1, 2, 4, 10 mL

4.3.2 Flocculation tubes (10 for each sample and control)

4.3.3 Flocculation tube racks

4.3.4 Sterile 50 and 100 mL screw capped bottles

4.3.5 Jar with disinfectant for used pipettes

4.3.6 Spatula

5. Procedure

5.1 Introduction

If an antigen and antibody are mixed in equivalent proportions, a complex is formed which will precipitate or flocculate. Tetanus toxin and toxoids, as well as AlPO4 absorbed tetanus toxoid vaccine where the gel can be dissolved and the toxoid released, will flocculate with specific proportions of a reference antitoxin. This is an immunological binding assay, not a biological potency assay. The test can also be used for determining the efficiency of absorption of toxoid to AlPO4 in tetanus vaccine by centrifugation of the AlPO4-bound vaccine and measuring the toxoid in the supernatant. The Lf of the supernatant is compared to the total Lf of the dissolved vaccine. A vaccine should have 80% or more of the toxoid absorbed.

5.2 Principle of the test.

The principle of the test is to incubate fixed amounts of toxin or toxoid with varying amounts of reference antitoxin, in the presence of an electrolyte, and recording the dilution which first flocculates. Kf is the time it takes to the first flocculation. For tetanus this is usually 20-40 minutes.

5.3 Safety precautions

5.3.1 Wear protective gloves, and mask when working with tetanus toxin.

5.3.2 In the production area, wear the required clean room dress.

5.4 Sample preparation.

5.4.1 No preparation is required for toxin or fluid toxoid. Absorbed toxoid must be released by dissolving the AlPO4 with sodium citrate to solubilize the toxoid. Lf cannot be quantitatively determined for toxoid bound to AlOH because it cannot be completely dissolved.

5.4.2 For absorbed vaccine, weigh out 0.5 g of sodium citrate and add to a vial of vaccine containing 5.5 mL. Incubate at 37°C for 24 to 48 hours until the aluminum phosphate gel has dissolved (solution is completely clear).

5.4.3 The standard tetanus toxoid vaccine which is used as a positive control in the test must be dissolved before use as described in 5.4.2.

5. Procedure, cont'd

5.5 Test procedure

5.5.1 Adjust water bath to 45°C.

5.5.2 Label the flocculation tubes 1-10 for each reference standard and sample to be tested: 1-1 to 1-10; 2-1 to 2-10, etc.

5.5.3 Pipette increasing amounts of the 100 Lf/mL reference antitoxin into each set of 10 tubes in the following amounts: 0.05; 0.10; 0.15; 0.16; 0.17; 0.18, 0.19; 0.20; 0.21, 0.22 mLs.

5.5.4 Prepare a dilution of the test toxin or toxoid to about 15-20 Lf/mL in saline solution based on the estimate of Lf/mL.

5.5.5 Prepare a dilution of the standard toxoid vaccine (dissolved as instructed in paragraph 5.4.3) in saline solution to 20 Lf/mL.

5.5.6 Add normal saline to each tube to bring the volume of each flocculation tube to 1 mL (ie 0.95 mL to tube 1 of each set, 0.90 mL to tube 2 of each set, etc).

5.5.7 Add 1 mL of diluted sample or standard vaccine to the respective set of 10 flocculation tubes. Add quickly to have the same start time for all tubes.

5.5.8 Mix thoroughly by gentle shaking of each tube.

5.5.9 Incubate all tubes in racks in the water bath with 1/3 of the reaction mixture immersed in the water of the waterbath.

5.5.10 Record the time and observe each vial closely for flocculation every 3 minutes.

5.5.11 Record the tube of each set which first shows flocculation, and record the time, Kf, of each sample.

5.5.12 Record the second and third tube showing flocculation for each sample set.

6. Reporting

6.1 Enter all data on Data Record Form # 321

6.2 Record all deviations to the procedure on the data record form.

6.3 Report to Supervisor if any problems occur during the test.

6.4 Sign completed data record form and deliver to supervisor for verification.

7. Reference Documents:

SOP ___: Operation, Maintenance, and Calibration of the WB Waterbath

SOP ___: Operation, Maintenance, and Calibration of the Balance, model B

SOP ___: Preparation of Sterile 0.85% Sodium Chloride Solution.

SOP ___: Preparation and Testing of the Reference Antitoxin

Data record form: *321* **Rev** *0* **Name of facility** *ABC Vaccine Manuf Co.* **page** *1* **of** *..5..*
SOP reference number: *ABC-3*

Lf FLOCCULATION TEST: TETANUS

Date: _____ Operator: _____

Test sample: Crude toxin [ ] Detoxified Toxoid [ ] Bulk Concentrate [ ]

Final Adj Bulk [ ] Final container [ ]

Lot/Batch number: Initial test [ ]

Repeat test [ ]: Reason: First assay invalid [ ]; First test failed [ ]

Preparation: **Note: for in-process tests in the clean room, the equipment, reagents and glassware must be prepared and approved for clean room use.**

A: Glassware and supplies checklist			
Item	**Amount required**	**SOP ref**	**Initials**
pipettes, 1 mL		SOP glassware cleaning and sterilization	
pipettes, 2 mL		"	
pipettes, 4 mL		"	
pipettes, 10 mL		"	
flocculation tubes		"	
flocculation tube racks		"	
50 ml. screw capped bottles, sterile		"	
100 ml screw-capped bottles,sterile		"	
disinfectant		SOP Preparation	
spatulas		NA	
gloves		SOP safety precautions	
masks		SOP safety precautions	

(06)

B. Equipment checklist				
Item	**Equipment Number**	**SOP ref**	**Calibration Date**	**Initials**
Waterbath		SOP #		
Lamp		NA		
Balance, model B		SOP #		
Clock/Timer		NA		
Convex lens		NA		

(07)

Lf Test for tetanus continued: Lot/Batch number _____ Date _____

C. Reagent checklist				
Item	**Lot#/expiry**	**SOP ref**	**QC approval date**	**Initials**
0.85% NaCl		SOP #		
ref antitoxin		SOP #		
standard tetanus vaccine		SOP #		
sodium citrate		SOP #		

(08)

Preparations verified by: _____

Procedure

A: Sample preparation:

Required for the reference standard tetanus vaccine and for AlPO4-absorbed test samples only.

1. Check water bath temperature is at 37 deg C _____ Initials _____ Verified _____
2. Weigh out 0.5 gms of sodium citrate for the reference standard tetanus vaccine and for each 5.5 mL of ALPO4-absorbed test sample.

   Weighed by _____

   Weights verified by _____

Item	**tare weight w1 (gm)**	**tare plus citrate w2 (gm)**	**weight of citrate w2-w1 (gm)**	**Add 0.5 gm to vaccine vial**
reference std tetanus vaccine				
test lot _____				

(09)

3. Incubate at 37 deg C for 24-48 hours

	Hr/min	Initials	Verified by
Time on	_____	_____	_____
Time off	_____	_____	_____
Elapsed time	_____	_____	_____

Elapsed time must be between 24-48 hours _____

Lf Test for tetanus continued: Lot/Batch number _____ Date _____

4. Set water bath temperature to 45 deg C

Initials _____Verified _____

5. Label tubes: reference std: 1-1 to 1-10 _____ _____
test sample 2-1 to 2-10 _____ _____

6. Prepare dilution of reference standard tetanus vaccine and test sample

a) reference standard tetanus vaccine to 20 Lf/mL

Lf/mL of vaccine _____ (A)
Volume of vaccine 1 mL
Volume of saline in mL (B)

Volume of saline to be added/1 mL vaccine: $B = \frac{(A - 1)}{20} =$ _____ mL

Dilution factor for vaccine = _____

b) test sample to 15-20 Lf/mL (17.5 av)

Estimated Lf/mL _____ (C)
Volume of sample 1 mL
Volume of saline in mL (D)

Volume of saline to be added/1 mL vaccine: $D = \frac{(C - 1)}{17.5} =$ _____ mL

Dilution factor for test sample = _____

Calculations Initials _____ Verified _____

7. Add first the ref antitoxin, then saline to the tubes as indicated in the table

Initials _____

Add one mL of the std vaccine to the first set of 10 tubes and the test sample to the second set of 10 tubes. Mix each tube by shaking gently

Initials _____

Lf Test for tetanus continued: Lot/Batch number _____ Date _____

Compontent Tube#	Volume in mLs									
	1-1	1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10
Ref antitoxin @ 100 Lf/mL	.05	.10	.15	.16	.17	.18	.19	.20	.21	.22
Saline, 0.85 %	.95	.90	.85	.84	.83	.82	.81	.80	.79	.78
Standard vaccine @ 20 Lf/mL	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

(10)

Compontent Tube#	Volume in mLs									
	2-1	2-2	2-3	2-4	2-5	2-6	2-7	2-8	2-9	2-10
Ref antitoxin @ 100 Lf/mL	.05	.10	.15	.16	.17	.18	.19	.20	.21	.22
Saline, 0.85 %	.95	.90	.85	.84	.83	.82	.81	.80	.79	.78
Standard vaccine @ 20 Lf/mL	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

(11)

8. Put racks of tubes in water bath with 1/3 of the reaction volume immersed in the water

   Time incubation started _____ Initials _____ Verified by _____

9. Observe each tube every 3 minutes for flocculation.

   Record the time of the first 3 tubes showing flocculation in the tables.
   Calculate Kf for first 3 tubes
   Kf = (time of flocculation) - (time incubation started)

REF STD VACCINE TUBE#	Volume in mLs									
	1-1	1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10
Antitoxin/tube (Lf/mL)	.05	.10	.15	.16	.17	.18	.19	.20	.21	.22
Flocculation #1,#2,#3										
Time flocculation seen										
Kf in minutes										

(12)

REF STD VACCINE TUBE#	Volume in mLs									
	1-1	1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10
Antitoxin/tube (Lf/mL)	.05	.10	.15	.16	.17	.18	.19	.20	.21	.22
Flocculation #1,#2,#3										
Time flocculation seen										
Kf in minutes										

(13)

Initials _____ Verified by _____

Lf Test for tetanus continued: Lot/Batch number _____ Date _____

10. Calculations

a) Standard tetanus vaccine:

Lf/mL of first tube to show flocculation _____

Lf/mL x dilution factor = Lf/mL of standard vaccine = _____

Acceptance criteria: 20 ± 3 Lf/mL:

Assay valid ____ Assay Invalid _____

b) Test sample:

Lf/mL of first tube to show flocculation _____

Lf/mL x dilution factor = Lf/mL of test sample = _____

Acceptance criteria: xx ± z Lf/mL: (will depend on the test sample)

Pass ____ Fail _____

11. Repeat test:

If the reference vaccine does not meet the acceptance criteria, the test is invalid and the full test is repeated.

If the assay is valid and the test sample fails to meet the acceptance criteria, the full test may [ ], may not [ ] be repeated.

12. Deviations to the procedure: No [ ] Yes [ ]

If yes, list deviations

Operator (technician) _____ Date _____

Verification (supervisor) _____ Date _____

Submit to QC or QA for review and approval of the data and deviations,if any.

QA/QC Review:

PASS _____

(signature, date)

FAIL _____

(signature, date)

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *2*

SOP Number *ABC-4* Title *Reporting of Production Incidents/Deviations and Resulting Actions*

Revision number *2* .

Written by _____ Edited by _____

Authorization signature _____ Department (QA/QC) _____ Date_____

Effective date *June 12, 1993* Replaces *Revision 1 dated: Aug. 20 1989*

1. Purpose

The purpose of this SOP is to describe the method for reporting production incidents and deviations from established written procedures, or deviations from established specifications and the actions taken.

2. Scope

This SOP applies to the Production Department.

3. Responsibility

3.1 It is the responsibility of the entire production staff, supervisors and manager to follow this procedure. The supervisor of each production section (facility operations, fermentation, purification) is responsible for any deviation, for the decisions taken following a production incident and for ensuring that the QA department is notified in a timely manner.

3.2 It is the responsibility of QA to review and update this SOP as required.

4. Materials and Equipment: None

5. Procedure

5.1: Definitions:

5.1.1 **Incident**: Brief excursion from specifications not directly affecting product quality, purity, or safety.

Examples: Process temperature briefly out of specifications; equipment malfunction not affecting the product (ie particle counter malfunction).

5.1.2 **Deviation**: Process parameter out of specification; product quality, purity or safety in question.

Examples: Yield, appearance, temperature, pH, flow rate, incubation time, fill volume out of specifications; contamination in inoculum; critical equipment malfunctions (ie autoclave); volume or product reconciliation problem .

5.1.3 **Critical Deviation**: Process performed incorrectly. Product quality, purity, safety affected. Examples: Incorrect reagent or concentration used; product mislabeled.

5. Procedure Cont'd

5.2: Procedure:

5.2.1 Document all incidents and deviations on Data Record Form # __.

NOTE: All incidents and deviations must be recorded and initialed at the time of the event in the batch processing records to indicate that an incident or deviation occurred. This note should describe the event and any corrective action taken. It must be initialed and dated by the appropriate supervisor

5.2.2 Corrective action should be recommended by the appropriate supervisor or superior. This person will approve by signing the process records.

5.2.3 Notification: The following persons must be notified:

Incident:
Supervisor - immediately
Dept Manager - Review
QA Manager - Review
VP Operations - NA

Deviation:
Supervisor - immediately
Dept Manager - immediately
QA Manager - immediately
VP Operations - Review

Critical Deviation:
Supervisor - immediately
Dept Manager - immediately
QA Manager - immediately
VP Operations - immediately

5.2.4. Records:

Form # ___ will be used by the production department to document the incident/deviation and the action taken.

Form # ___ will be used by QA to maintain a log of incidents/deviations and to assign a sequential number to each event.

QA will follow-up the recommendations for action and prepare a final report when the recommendations have been implemented.

QA will file the original report in the QA files and send a copy to the production department.

6. Reference Documents

Data Record Form # _____: Incident/Deviation Report.

Data Record Form # _____: QA Doc: Incident/Deviation Report Log

Data record form: *zzz* **Rev** *2* **Name of facility** *ABC Vaccine Manuf Co.* **page** *1* **of** *..2..*
SOP Number: *ABC-4*

INCIDENT/DEVIATION REPORT

Report #: _____

Department:_____

Date:_____

Reported by: _____

Incident [ ] Deviation [ ] Critical Deviation [ ]

Date of occurrence:_____

Component/intermediate/product/lot number affected: _____

1) Description of incident/deviation (include process, lot number, which production step, result):

2) Number of previous occurrences to same product over previous year (dates, lots affected):

3) Action taken (who was notified, when, who approved action, what was done, previous actions for previous occurrences):

4) Justification for action (previous events, literature, advice of superiors, identity of superiors):

5) Significance of event on process or product (effect on yield, recovery, stability):

6) Remedial action to prevent re-occurrence (ie revise SOP or datasheets/record forms, retrain personnel, repair or revalidate equipment):

INCIDENT/DEVIATION REPORT

Report prepared by Date:_____

Corrective action approved by:_____ Date:_____

Reviewed by: :_____ Date:_____

Reviewed by::_____ Date:_____

QA Reviewer::_____ Date:_____

QA Comments and recommendations:

QA Follow-up (recommendations completed?)

VP Operations Review::_____ Date: _____

Date Report Finalized::_____ QA: _____

Data record form: _ttt_ **Rev** _2_ **Name of facility** _ABC Vaccine Manuf Co._ **page** _1_ **of** _..1.._
SOP reference number: *ABC-4*

QA: Incident/Deviation report log						
Report #	**Date**	**Dept**	**Classifi-cation**	**Product**	**Lot #**	**Description**

(14)

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *2*

SOP Number *ABC-5* Title *Responsibilities of Quality Operations (QO) Departments .*

Revision number 0

Written by _____ Edited by _____

Authorization signature _____ Department (Management) _____ Date ____

Effective date *April 12, 1995* Replaces *new*

1. Purpose

This SOP describes the basic responsibilities of Quality Operations at the ABC Vaccine Manufacturing Company.

2. Scope

This SOP applies to all Quality Control and Quality Assurance staff of the company.

3. Responsibility

The QO Director, the QC Manager and the QA Manager are responsible for following this SOP and for revising the SOP as needed.

4. Materials and Equipment

None.

5. Procedure

5.1: QC Responsibilities

5.1.1 The QC department has the responsibility and authority to approve or reject all components (raw materials), drug product containers, closures, in-process materials, packaging materials, labeling, and drug products.

5.1.2 The QC department has the responsibility and authority to provide adequate laboratory test facilities to test and accept or reject components and the container-closure system, and delivery system, if attached, to be used in the manufacture, processing, packing and holding of the intended parenteral drug product. The QC department has the authority to reject such a system if it does not comply with the provisions of this part, or if, in the opinion of the QC department, it is not capable of holding the product invulnerable to contamination under the intended or contemplated conditions of shipment, storage and use.

5.1.3 The responsibilities and procedures applicable to the QC Department are in writing and such written procedures should be followed.

5. Procedure, Cont'd

5.2: QA Responsibilities

5.2.1 The QA Department has the responsibility and authority to accept or reject the design, engineering, and physical facilities of the plant, the equipment, the manufacturing process and control procedures to be used in the manufacture, processing, packing, and holding of each parenteral drug product. The QA Department has the authority to reject any such plant equipment process or procedure if it does not comply with the provisions of this part or if, in the opinions of the QA Department, it is not suitable or adequate to assure that the drug product has the characteristics it purports or is represented to possess.

5.2.2 The QA Department has the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, purity and stability of the drug product.

5.2.3 The QA Department has the responsibility and authority to approve or reject any changes in previously approved plant, equipment processes, procedures, and container-closures and delivery systems before utilization in the manufacture, processing, packing, and holding of a parenteral drug product.

5.2.4 The QA Department has the authority to review production records to assure that no errors have occurred, that they have been fully investigated.

5.2.5 The QA Department has the responsibility and authority to handle the "certification/ calibration" programme of major equipment.

5.2.6 The QA Department has the responsibility and authority to review the QC testing records.

5.2.7 The responsibilities and procedures applicable to the QA Department are in writing and such written procedures should be followed.

6. Reference Documents

(the relevant National or International GMP Guidelines)

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *3*

SOP Number *ABC-6* Title *Quality Audits, General*

Revision number *2*

Written by _____ Edited by _____

Authorization signature _____ Department: *QA* Date _____

Effective date *May 12, 1994* . Replaces *Revision 1 dated: April 12 1992*

1. Purpose

The objective of this SOP is to describe the method of auditing departments in order to ensure compliance with regulations and guidelines, as well as internal standards and policies. The purpose of an internal audit is to monitor the production and quality control departments for compliance with GMP, regulatory and product quality requirements and to recognize and address any deficiencies. A Contract Manufacturing Audit is an evaluation of facilities and systems operated by another company which performs part of the manufacturing process (ie bulk product, or final filling). A Vendor Audit is an evaluation of a supplier of raw materials or other products and components purchased for use in production.

2. Scope

This SOP applies to all audits conducted by the Quality Assurance Department. It includes audits of all internal departments associated with ABC Vaccine Manufacturing Company's production facility, Contract Manufacturers, and Vendors. It does not include record reviews which are described in SOP #_____.

3. Responsibility

3.1 It is the responsibility of the Quality Assurance Department to inspect departments at least annually to ensure compliance with national or international regulations and guidelines, as well as internal standards and policies. QA is also responsible for auditing contract manufacturers and vendors, as needed. It is also this department's responsibility to document each auditing event.

3.2 It is the responsibility of each department to provide access to their facilities at QA's request. Each department is also responsible for responding in writing within 30 days to QA recommendations for action to be taken.

3.3 It is the QA Manager's responsibility to review and revise this SOP as necessary.

4. Materials and Equipment

As required for each type of audit.

5. Procedure

5.1 Philosophy:

The purpose of an audit is to evaluate the systems, processes and functions of a department as a team. It should not be considered as a personal evaluation or critique. The department personnel together with the auditors will determine the course of action to improve compliance with the applicable regulations and guidelines.

5.2 Preparation for Audit:

5.2.1 Review the last internal audit and National Control Authority inspection reports. Note the citations and comments so that these can be evaluated during the audit.

5.2.2 Contact the department for a work schedule and agree on meeting dates.

5.3 Audit:

5.3.1 The audit is to take place during normal working hours. If production is performed during several shifts, special emphasis should be placed on conducting audits during shifts when the level of supervisory staff is reduced.

5.3.2 During the audit, it is important to work in cooperation with department personnel. It is also important to get as much information as possible about the current procedures by

a. Asking open-ended questions
b. Listening and understanding
c. Restating responses
d. Allowing time for responses
e. Showing flexibility and a constructive attitude
f. Choosing proper vocabulary

5.3.3 The audit is to be carried out using the approved audit checklist.

5.4 After Audit:

5.4.1 The QA auditors will write up an official report of the findings on the department. These comments will be classified as follows:

a. **Critical**: a problem that directly affects the product, for example:
    1. open sterile products in a non-aseptic area
    2. no traceability of components
b. **Major**: a problem that may affect the product, for example:
    1. equipment not calibrated
    2. untrained operators
c. **Minor**: an issue that does not directly affect the product, for example:
    1. crossouts and corrections not initialed or dated

5. Procedure, Cont'd

5.4.2 The auditors will hold a meeting with the department personnel to discuss the findings and agree on improvements to be made.

5.4.3 The department will respond to the findings with the improvements to be made and their expected completion dates.

5.4.4 The auditors will follow up on those issues to ensure that they are being resolved and that compliance has improved. A follow-up report will be prepared.

5.4.5 The QA department will maintain a log of all audits

5.5 Frequency of audits

QA will schedule an announced audit for each department at least once per year. A rolling 6 month schedule of audits is considered ideal. Unannounced audits may occur at any time. When outside regulatory authorities inspect the facilities, QA should also write up their own report and meet with the departments as outlined in section 5.4.

6. Reference Documents:

6.1 SOP #___: Batch Record Review

6.2 SOP #___: Quality Assurance Self Inspection

6.3 Data Record Form #__: Quality Assurance Audit Log

6.4 Relevant GMP guidelines and regulations regarding self audits and outside audits.

Data record form: *xyz* **Rev** 2 **Name of facility** *ABC Vaccine Manuf Co.* **page** *1* **of** *..1..*
SOP reference number: *ABC-6*

Quality assurance audit log				
Year				
Audit No.	**Department Contractor Vendor**	**Audit dates**	**Meeting date**	**Date of response**

(15)

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *4*

SOP Number *ABC-7* Title *Method for Sampling Raw Materials and Production Components*

Revision number *0*

Written by _____ Edited by _____

Authorization signature _____ Department (QA/QC) _____ Date _____

Effective date *May 12, 1994* . Replaces *new* .

1. Purpose

The purpose of this SOP is to describe the method for sampling and testing raw materials and other production components.

2. Scope

This SOP applies to the Receiving/Warehousing and Quality Control Departments.

3. Responsibility

3.1 It is the responsibility of the Receiving/Warehousing Department and the Quality Control Department to follow this procedure.

3.2 The Quality Control Manager is responsible for ensuring that this procedure is followed.

3.3 It is the responsibility of QC to review and update this SOP as required.

4. Materials and Equipment

(Need to give the specifics of the sampling equipment and supplies, sampling hoods/booths/areas in the warehouse area)

5. Procedure

5.1 General Requirements:

5.1.1 Handling and storage of the materials must ensure prevention of contamination.

5.1.2 Bagged or boxed materials are stored off the floor (on shelves or on pallets) and are suitably spaced in order to permit cleaning and inspection.

5.1.3 Each container or grouping of containers for raw materials or drug product containers or closures, are identified with a distinctive code number for each lot in each shipment received. This code is used in recording the disposition of each lot. Each lot is identified by a coloured sticker as to its status as follows:

Yellow sticker	Receiving/Quarantine
Green sticker	Released
Red sticker	Rejected

5. Procedure, *Cont'd*

5.2 Receipt and Storage of Materials requiring Testing or Examination by QC:

5.2.1 Upon receipt and before acceptance, each shipment is examined visually as to its integrity and proper labeling. This inspection is performed by the warehouse operator in the receiving area, who applies the yellow stickers, containing all necessary details:

- Date
- Company code number
- Receiving number
- Package number (of total)
- Supplier's lot number

5.2.2 Materials are stored under quarantine until tested or examined, and released or rejected by Q.C. For each material, the Q.C. reviews the "entry" documents, the yellow stickers and a copy of the certificate of analysis, if available.

5.3 Sampling:

5.3.1 Representative samples of each shipment of each lot are collected for testing or examination by the Q.C. operator. Quantity of sample should be at least three times that needed to perform all tests other than for sterility and pyrogen testing (single test)

For solid materials: Less than 250g 5-15% of weight
250-5000g 2.5-10% of weight
>5000g 125-260g
For liquid materials: samples are taken into clean test tubes.
Samples are taken according to a sampling plan (see Appendix).

5.3.2 Sampling is performed in a way designed to prevent contamination. Sterile equipment and aseptic sampling techniques are used when necessary.

5.3.3 If it is necessary to sample a raw material from the top, middle and bottom of its container, such samples are not mixed for testing.

5.3.4 Sampled containers are identified by a specific “sampled” sticker containing the date and name of operator.

5.4 Testing and Approval or Rejection:

5.4.1 At least one test is conducted to verify the identity of each raw material. Identity tests are performed according to monographs appearing in the USP, EP, WHO or other accepted methods.

5.4.2 When no official monograph exists, an internal SOP is prepared.

5. Procedure, Cont'd

5.4.3 Each raw material is tested for conformity with all appropriate specifications for purity, strength and quality. If the tests are conducted by the manufacturer or supplier of the raw material, a certificate of analysis is required. For raw materials which are intended to be a part of a finished Product, tests for purity, strength and quality are performed by the Q.C., according to tests appearing in existing monograph (USP, EP, WHO or BP).

For suppliers who have been audited and approved by QA, only the identity test is required to be performed by QC.

5.4.4 When the tests performed by the Q.C. lab are completed, the documentation is signed and transferred back to the warehouse for release (or rejection). The Q.C. operators are responsible for applying the green (or red) stickers.

5.4.5 In the Q.C. lab, there is a separate file for each raw material, drug product container or closure, where the test results and copies of the documentation are filed.

5.5 Retesting:

In accordance with shelf-life requirements for raw materials (determined by the QC department), raw materials are retested periodically. A list of raw materials for retesting, its time table and types of tests, is attached to the general list of raw materials used for manufacture of each drug product. A Raw Material Retest Record Sheet is prepared and a dated and signed retest sticker is applied by the Q.C. operator on each retested package.

5.6. Retention Samples:

A well identified sample of each raw material tested and released is set aside for retention in a specified, labeled storage location (except for volatile or evaporating materials).

6. Reference Documents:

Annex 1: Raw Materials Sampling Plan.

Data Record Form # ___: Receiving Entry Log

Data Record Form # ___: Raw Materials Inspection and Sampling Report

Data Record Form # ___: Raw Material Retest Record

Annex 1: RAW MATERIALS SAMPLING PLAN (Ref: Mil-Std-105D)

The following schedule is recommended for sampling.
Number of Containers or Units to be Sampled per Lot or Batch in each Shipment

A. Active raw materials	
No of containers in shipment	**Number to be sampled**
2-15	2
16-25	3
26-90	4
91-150	8
151 and over	13

16

B. Inactive raw materias and primary packaging components	
No. of containers or units	**Number to be sampled**
2-8	2
9-15	3
16-25	5
26-50	8
51-90	13
91-150	20
151-280	32
281-500	50
501-1200	80
1201-3200	125
3201-10000	200
10001-35000	315
35001-150000	500
150001-500000	800
500001 and over	1250

17

C. Other packaging components	
No. of packages in shipment	**Number to be sampled**
2-15	2
16-50	3
51-150	5
151-500	8
501-3200	13
3201-35000	20
35001-500000	32
500001 and over	50

18

9.2 Content requirements for SOPs for several types of procedures

(i) Entry and Exit: Clean and Sterile Production Areas

(ii) Internal Inspection Procedures

(iii) Control of Biological Starting Materials

(iv) Environmental Monitoring of Cleanrooms: Sampling Method

(v) Label Control and Issuance

(vi) Procedure for Cleaning

(vii) Specification Sheets for Raw Materials

(i) SOP: ENTRY AND EXIT

EXAMPLE: Entry and exit of people, supplies, starting materials, product intermediates when they are stored outside the cleanrooms, and exit of QC samples for in-process tests, and removal of wastes must follow defined procedures and be documented where necessary. SOPs must be prepared for each entry/exit point (e.g.: personnel entry room/airlock, pass-through, equipment entry airlock). Airlock entries are cleaned during routine cleaning programme and controlled by the environmental monitoring programme therefore the entry procedure does not include these operations. Pass-throughs for supplies must include decontamination procedure before and after transfer.

SOP ___: Personnel Entry and Exit: Clean and Sterile Production Areas

1. Purpose

To provide detailed instructions for gowning and entry into cleanrooms.

2. Scope

Describe the location of each cleanroom area where the procedure applies. Indicate that the instructions must be followed by all persons entering the production areas every time they enter and exit.

3. Responsibility

Authorized production staff, hired cleaning staff, building cleaning staff, and any person specifically authorized by the production manager to enter the production area, must follow these instructions.

The production manager is responsible for ensuring the procedure is followed.

4. Materials and Equipment

Describe the facilities in the entry rooms (lockers, showers, shoe racks, dividing bench, etc.). List the garments, disinfectants, and other materials used in the entry airlock.

disinfectant soap
cleanroom entry log book
sterile masks
sterile gown
sterile gloves
sterile head covers
sterile shoe covers
cleanroom shoes
alcohol spray
garment disposal bag or bin

(i) SOP: ENTRY AND EXIT, continued

5. Procedure

a) Preparation

- describe the preparation of disinfectant soap such as dilution, rotation etc.
- describe procedure for changing from street clothes to lab clothes for non-critical areas.

b) Entry procedures. Clear instruction for the following:

- instructions for signing entry log book
- describe clothes and ornaments to be removed and where to store.
- describe showering or washing required
- describe order of putting on cleanroom garments
- describe use of alcohol spray during the gowning process
- describe the final step of donning shoe covers and stepping over bench
- describe precautions to prevent contamination of gloves during entry into clean room.

c) Exit procedures.

- describe the removal and disposal of each garment
- refer to the SOP for personnel monitoring (swabs) on exit.
- signing out in the log book
- describe showering or washing if required.

6. Reporting

An Entry Exit Log Sheet of Log Book should be prepared to record staff, dates and times. Identify what information needs to be included in the Entry/Exit Log.

7. Reference Documents

References to other SOP documents that are needed to perform parts of the cleaning operation. For example:

SOP for Cleaning of Garments.
SOP for Disinfectant Testing
SOP for Personnel Monitoring.

(ii) SOP : INTERNAL INSPECTION

EXAMPLE: General requirements of an SOP written for the process of performing a QA Audit/ Self Inspection.

SOP _____: Internal Inspection Procedures

1. Purpose

To describe the self inspection method to ensure compliance with WHO GMP guidelines.

2. Scope

The inspection of all internal departments associated with vaccine manufacture.

3. Responsibility

- Indicate that the QA department is responsible for auditing the facility at least once a year, fully documenting the inspection and preparing a written report with the recommendations and actions required for improvement for each department.
- Also state that it is the responsibility of each department to provide access to the QA investigator and to respond to any actions stated in the QA inspection report within a predetermined time period after the receipt of the written report.
- Indicate that QA must then re-inspect to determine if the corrected action is satisfactory and report these comments.
- State that the QA manager is responsible for keeping the SOP current.

4. Materials and Equipment As required.

5. Procedure: Indicate clearly the following steps:

a) **Principle:** Evaluate systems, processes and functions of a department to determine whether actions are required to improve compliance with the guidelines.

b) **Preliminary**:

- Prepare, or ensure that the QA checklist is prepared.
- Review earlier (internal or external) inspections, reports actions required, actions taken and any comments that would indicate specific items to be inspected.
- Set up schedule for each department for the date and time of the annual audit.
- Unannounced audit can be made at any time.

(ii) SOP : INTERNAL INSPECTION, continued

5. Procedure, continued

c) **Audit:** Using prepared checklist to go through the departments:,

- Reviewing the premises (state of repair, cleanliness, env monitoring data, etc.),
- Appropriate attire worn in each area,
- Appropriate personnel behaviour in specific areas,
- Equipment (state of repair, cleanliness, logbooks, calibration), preventive maintenance),
- Records and documents for completeness, accuracy, dating and signatures.
- Signs and labels are clear and accurate,
- Traceability of components,
- Training files,
- Appropriate control of open products
- Appropriately segregated storage.
- Inspection of the production areas should be done from outside the area wherever possible:

d) **Report:** Make a report of the non-compliant items, and propose actions to be taken. Note especially critical problems such as breaches in aseptic procedures, or documents inadequate for traceability.

6. Reporting

- Checklist is to be used to document the initial findings and to identify what areas need to be improved.
- This must be expanded in a detailed written report.
- There should be a time limit for the presentation of the report
- There should be a time limit for each department to comply with an action request
- There should be a scheduled follow-up inspection especially for serious problems.

7. Reference documents

- References to other SOP documents
- WHO GMP Guidelines

(iii) SOP: BIOLOGICAL STARTING MATERIALS

EXAMPLE: For every cell, bacteria and virus used to manufacture the vaccine, there must be testing, verification and documentation of the original strain, stocks and inoculation materials to ensure the quality for use in production.

SOP____ : Control of Biological Starting Materials

1. Purpose

To describe the information required, to identify and characterize stocks and inoculation materials for production of vaccines.

2. Scope

For all cells, virus, bacterial strains used in the manufacture or testing of vaccines. To be prepared for all new stocks and revised for existing stocks if any changes in the storage or maintenance occur.

3. Responsibility

Production should prepare a record for each stock.

QC is responsible for reviewing and approving the specifications.

4. Materials and Equipment

As required (computer, logbooks, record sheets, etc.).

5. Procedure

a) Record the name, source, history, date received, passage level, growth medium, storage medium, state (lyophilized or liquid culture) and any other relevant details of the original strain.

b) Record the dates of the approval of the strain by the national control authority.

c) Record the tests required, tests performed and results (in house results or results provided with the strains).

d) Provide details of the seed lot system used to create the seed lots (primary or secondary) and cell banks (master and working):

Growth medium
Freeze medium
Storage conditions
Number of passages
Pooling, aliquoting
Number of aliquots for each seed lot or cell bank
(Refer to WHO TRS for each vaccine for the required details)

(iii) SOP : BIOLOGICAL STARTING MATERIALS, continued

5. Procedure, continued

e) Provide list of tests to be performed to characterize the seed lots or cell banks, including stability tests.

f) Attach results of characterization tests or give location of characterization files, including QC approval.

g) State location of the inventory log or computer file which records the disposition of the seed lots or cell banks.

h) List the tests and specifications for characterizing the working stock performed before inoculating a production run. Give the SOP numbers for the test procedures (refer to WHO TRS for each vaccine for the recommended tests).

i) List the schedule of periodic retesting of seed lots and/or cell banks as appropriate for the respective type.

6. Reporting

An appropriate record sheet should be prepared for each type of strain. The completed record sheet to be kept on file, and updated by production department as required.

7. Reference Documents

WHO TRS for each specific vaccine (sections on cell and seed stock controls)

SOPs for characterization methods.

SOPs for relevant QC release tests.

(iv) SOP: SAMPLING FOR ENVIRONMENTAL MONITORING

EXAMPLE: General requirements for an SOP written for taking the samples for environmental monitoring.

SOP ___: Environmental Monitoring of Cleanrooms: Sampling Method

1. Purpose

To provide a complete description of the methods and schedules for taking samples for monitoring the air and surfaces (including personnel) in all production areas for non-viable and viable counts to ensure compliance with predetermined cleanliness levels.

2. Scope

For taking the required samples for the routine monitoring of all classified, clean and aseptic areas of vaccine production.

3. Responsibility

a) QC tests and approves materials for monitoring microbial (viable) counts.

b) Production department responsible for performing the sampling procedures.

c) QC or QA is responsible for testing microbial count and reporting results.

d) QA is responsible to ensure procedure is followed. and to investigate if acceptable levels are exceeded.

4. Materials and Equipment

List swabs, contact plates, settling plates as appropriate.

Particle counter (electronic or vacuum apparatus with filter trap)

Microbial sampling apparatus.

Disinfectant for decontaminating surfaces of wrapped plates or swabs.

Chart of sampling locations for each room.

5. Procedure:

a) Principle: Cleanliness classes are an accepted requirement in the manufacture of biologicals. All GMP guidelines specify critical aseptic areas (exposed sterilized components and drug product, eg during filling) and controlled areas (all production and preparation of unsterilized product and components).

b) Specify the safety precautions to be taken during monitoring (e.g. aseptic handling).

c) Preliminary steps. Provide details of:

Floor plans of rooms and sampling locations identified.
Schedule and frequency of monitoring of rooms and personnel according to room function.
Requisition of appropriate number of plates from QC in advance.
Monitoring equipment maintenance and calibration verified.

(iv) SOP: SAMPLING FOR ENVIRONMENTAL MONITORING, continued

5. Procedure, continued

d) Day of sampling: Give step-by-step instructions for the following:
Delivery of sealed sterile plates or swabs by QC to the pass-through with record sheet.
Decontaminating outer surfaces of packaging in pass-through before entering clean area.
Checking plates/swabs for sterility (no visible growth).
Transporting labelled plates/swabs to locations indicated on the schedule chart.

e) Microbial Sampling of air and surfaces including personnel.

Give details for
Unwrapping plates or swabs.
Marking with date, time, room number, initials, location code, other identification.
Specific instructions for taking swabs or exposing plates.
Rewrapping after completion of sampling.
Advising QC and returning to QC via the pass-through.
Completion of the Production Section of the Data sheet.

f) For counting of non-viable particles (production)

Give detailed instructions for particle counting method used.
Give methods of calculating the particle count from the data.

6. Reporting

Fill in record sheets indicating any deviations to the sampling schedule or procedure.

Electronic particle count data from cleanrooms are to be recorded and reported to QA .

7. Reference documents

Depending on the methods used, list other relevant SOPs or reference documents that are used for environmental monitoring assessment.

SOP: __ Operation, maintenance, and calibration of the air sampler.
SOP: __ Operation, maintenance, and calibration of the particle counter.
SOP: __ Moving of plates/swabs in and out of a controlled or critical area.
SOP: __ Preparation of plates and swabs for environmental monitoring of clean rooms by QC.
SOP: __ Plate and swab counts: incubation and assessment by QC.
SOP: __ QC procedure for qualification of media used for environmental monitoring.
SOP: __ QC procedure for identifying and quantifying microorganisms found during environmental monitoring.
SOP: __ QC evaluation of environmental monitoring samples

(Acceptance criteria must be established for surfaces and personnel. For air see reference document FED-STD-209E. Alert and action levels, and procedures to follow if these levels are reached e.g. report to supervisor, report to QA, stop production, quarantine product, complete incident/deviation report, perform an investigation, must be defined prior to proceeding with the monitoring.)

SOP: __ Training procedures for good cleaning practices.
SOP: __ Entry, exit and gowning procedures for cleanrooms.
SOP: __ Monitoring schedule for cleanroom temperature and humidity, air flow, air balance and air pressures, and door and air lock function.
SOP: __ Cleaning and disinfection of cleanrooms.
WHO GMP for Pharmaceutical Products, TRS 823, 1992
FED-STD-209E: Standards and Methods for Particle Counting of Classified Cleanrooms.

(iv) SOP: SAMPLING FOR ENVIRONMENTAL MONITORING, continued

ENVIRONMENTAL MONITORING: SCHEDULE FOR SAMPLING

On a floor plan of each room requiring monitoring, identify the sampling locations, surfaces and equipment for air and surface monitoring and assign a code number to be used for the following tables. Indicate the frequency as daily, weekly, bi-weekly, depending on the activity and classification of the room.

A. Air monitoring					
Room#	Class	Viable air sampler		Particle sampling	
		Location	Frequency	Location	Frequency
19					

B. Surface monitoring					
Room#	Class	Surface sampling		Equipment sampling	
		Location	Frequency	Location	Frequency
20					

(iv) SOP: SAMPLING FOR ENVIRONMENTAL MONITORING, continued

EXAMPLE: ENVIRONMENTAL MONITORING DATA RECORD SHEET

A: Surface Monitoring, Viable Counts

QC to Complete and deliver with Materials:

Media Type (contact plate or swab type): .

Lot#: _____ QC release date: _____Exp. date: _____

Production to Complete _____ QC to Enter Test Results: SOP _____

Date of Sampling: _____ Date of Results: _____

Operator performing the sampling: _____

Room number	Activity	Location code	Results CFU	Colony ID	Performed by
[21]					

B: Personnel Monitoring, Viable Counts

QC to Complete and deliver with Materials:

Media Type (contact plate or swab type): _____

Lot#: _____ QC release date: _____Exp. date: _____

Production to Complete ***QC to Enter Test Results:*** SOP _____

Date of Sampling: _____ Date of Results: _____

Operator performing the sampling: _____

Staff Name	Location (chest, mask, gloves, other)	Performed by	Results CFU	Colony ID	Performed by
[22]					

(v) SOP: LABEL CONTROL AND ISSUANCE.

EXAMPLE: Final product labels must be under strict control and be reconciled before and after every use. This is a critical operation for any manufacturer to ensure that the correct labels with the correct lot number and expiry date have been applied to the final container. Therefore, there should be accurate records of all label usage from purchase orders, receiving counts, issuance counts, and individual label reconciliations.

The same control is applied to product boxes or cartons and package leaflets. This example discusses only labels for the final vials or ampoules.

SOP ___: Label Control and Issuance

1. Purpose

To describe the system for the complete and accurate control of all final product vial labels and their reconciliation.

2. Scope

Applies to all final product vial labels that are used in the Labelling and Packaging Department.

3. Responsibility

Indicate the persons or departments responsible for label control and issuance for the organization .

4. Materials and Equipment

Storage boxes

Secure storage location for labels

5. Procedure

The actual procedure will depend on whether the product lot number and expiry date are stamped by hand or automatically by the labelling machine.

a) Purchasing/Receiving enters shipment information for preprinted (excluding lot no. and expiry date) labels into receiving log according to the SOP, stores in quarantine, and informs QC.

b) QC checks labels against specifications and approves or rejects the shipment (SOP # __), and delivers to person responsible for storing and distributing labels.

c) Prepare a Label Reconciliation Form for each lot of labels. Keep a running balance on the form as the labels are used. (This form is for controlling large quantities of labels which are issued in smaller amounts for many different lots of the same product)

(v) SOP: LABEL CONTROL AND ISSUANCE, continued

5. Procedure, continued

d) Prepare an Issued Label Control Form on receipt of a request from the Labelling/Packaging Department for labels for a specific product. (The Issued Label Control Form remains with the issued labels to provide control of their use.)

e) Prepare the required and extra labels for each request.

Quantity Requested:	Additional Provided:
1-300	5
301-750	10
751-1,000	15
1,001-3,000	20
3,001-5,000	25
5,001	+ 1/2%

f) Verify the label count by two individuals; put labels and the Issued Label Control Form into label control boxes or envelopes.

g) Complete the Label Reconciliation Form, after the labels are printed, to record the amount requested by the Labelling/Packaging Department on the Label Control Form.

h) Deliver the labels and IssuedLabel Control Form to the Labelling/Packaging department (by QA inspector or other designated person).

i) If additional labels are required, the Labelling/Packaging Department must request the required number of additional labels on the Issued Label Control Form; and the additional labels are added into the Label Reconciliation Form by the QA and Labelling/Packaging Department personnel.

j) At the end of the day return any unused labels to the label secure storage. Person responsible signs for the labels.

k) Label Reconciliation

When labelling is finished, the Labelling/Packaging Supervisor completes the Issued Label Control Form by filling in the number of labels used for the following items:

(a) number used for Issued Label Control Form

(b) number used for boxes

(c) number used for final containers

(d) number damaged during labelling operations or unused labels

The total number of labels used and destroyed must equal the total number printed and issued.

(v) SOP: LABEL CONTROL AND ISSUANCE, continued

EXAMPLE: Issued Label Control Form

PRODUCT NAME _____

PRODUCT CONTROL NO _____ PRODUCT LOT NO _____

PRODUCT EXPIRATION DATE _____

Issuing department	Labelling/Packaging department
Label issued by: _____ Date: _____ Label checked by: _____ Date: _____ Control number: _____	Number received: _____ Received by: _____ Date: _____ Additional received: _____ Received by: _____ Date: _____
Total issued: ._____ Addt'l issued: _____	Number used: _____ For batch record: _____ for containers_____ for boxes _____ Number of additional used: _____ For batch record: _____ for containers _____ for boxes _____
Total issued:_____ Amount returned:_____ Returns counted by:_____ Date: _____ Amount destroyed: _____ Destroyed by: _____ Date: _____	Amount returned: _____ Amount damaged: _____ Returned by:_____ Date: _____

23

(v) SOP: LABEL CONTROL AND ISSUANCE, continued

Label Reconciliation Form

PRODUCT NAME _____

LABEL SIZE _____

SUPPLIER _____ P.O. # _____

COMPANY CODE # _____

RECEIVING # _____

QUANTITY ORDERED _____ QUANTITY RECEIVED _____ DATE _____

QC RELEASE DATE _____

INVENTORIED BY _____ DATE _____

CHECKED BY _____ DATE _____

Starting balance	Amount removed	Balance	Withdrawn by	Date	Checked by	Date

24

(vi) SOP: CLEANING

EXAMPLE: General requirements of an SOP written for any of the following processes:
Facility Cleaning: floors, walls, ceilings, work and equipment surfaces, etc.
Equipment Cleaning/Sanitizing: CIP, COP, SIP, washing the inside of blenders, filters, and tanks, etc.
General Glassware and Lab ware Cleaning: by hand or by automatic washer, etc.

SOP ___: Procedure for Cleaning

1. Purpose

To provide detailed instructions for the specific cleaning procedure.

2. Scope

Describe where this particular procedure is to be performed (in a controlled or general area, on specific equipment or in a specific room, etc.).
Indicate when the procedure is to be performed and how often it must be performed. (Everyday at 2 PM, once a week etc.)

3. Responsibility

State who is responsible for performing the procedure whether it be production staff, hired cleaning staff, building cleaning staff, etc.
State the title of the manager responsible for ensuring the procedures are followed.

4. Materials and Equipment

List the materials needed to complete the procedure, including the whole range of materials, equipment and utilities. The following are a few examples of the types of items one might include in this list:

Cleaning agents or disinfecting agents to be used
Swabs, cloths, mops, buckets, hosing, etc.
Vacuum cleaner
Automatic dishwasher

5. Procedure

a) the preparation of cleaning agents or detergents such as dilution, rotation etc.
b) safety precautions for any toxic agents being used
c) dress code required
d) clear and concise step by step instructions for the entire cleaning operation - number of washes, number of rinses, drying method, disposal or regeneration of cleaning materials.

6. Reporting

Identify what information needs to be documented, before, during or after the cleaning procedure, and where it is to be recorded. See example of a Cleaning Log, below.

(vi) SOP: CLEANING, continued

7. Reference Documents

References to other SOP documents that are needed to perform parts of the cleaning operation.
For example:
SOP for storage of cleaning agents.
SOP for gowning
SOP for the moving of equipment in and out of a clean or aseptic area
SOP for the operation of an automatic dishwasher, or vacuum cleaner

(vi) SOP: CLEANING, continued

Cleaning Operation Log

Operation Description: .

Fill in the date, time, product, cleaning agents before entering, fill out name after cleaning is complete

(vii) SOP: RAW MATERIALS SPECIFICATION SHEETS

EXAMPLE: Specifications list for each raw material or component to be used in production or quality control testing of product.

SOP _____: Specification Sheets for Raw Materials

1. Purpose

To describe the requirements for preparation of a specification sheet for raw materials.

2. Scope

Specifications are required for each raw material (chemical or biological), packaging component (vials, stoppers, seals, labels, leaflets) or any other material which comes in contact with the drug during manufacture (tubing, tanks, centrifuge bottles, storage containers, filters, pipe valves, syringes, replaceable caps, etc.).

3. Responsibility

a) The department requiring the material is responsible for setting the specifications.
b) QA is responsible for approving the specifications and approving the suppliers of the material.
c) The QC department is responsible for testing or assessing each material against the set specifications before it can be released for use in production, packaging, or for QC tests.
d) The QA Department is responsible for assigning an in-house code number to each material.

4. Materials and Equipment : None

5. Procedure :

Prepare a Raw Materials Specification Sheet for each material from data provided.

a) the approved name of the product (common chemical where appropriate) any alternate names and in-house code number.
b) the chemical composition, formula, weight, size or other description as appropriate.
c) indicate the quality or grade of product.
d) list the specific characteristics to be tested including the specifications.
e) list the SOPs of the test procedure(s) to be used to determine if the material meets specifications.
f) list of approved supplier and alternate suppliers, catalogue number or other specific identification number.

6. Reporting

Provision of the Raw Material Specification List to the Purchasing/Receiving Department for ensuring that materials of the correct quality are ordered from approved suppliers and that incoming materials are appropriately quarantined until released by QC.

(vii) SOP: RAW MATERIALS SPECIFICATION SHEETS, continued

7. Reference Documents

SOP __: Supplier Audit and Approval
References to accepted standard methods (eg):
Pharmacopeia,
WHO manuals

(vii) SOP: RAW MATERIALS SPECIFICATION SHEETS, continued

Raw Material Specification Sheet

A:

Approved Name: _____ In-house Code Number: _____

Alternate Name: _____

Formula: _____ Weight: _____ Size: _____ .

Quality or Grade _____

Description:

Storage conditions: _____

Approved Suppliers and product catalogue number

_____ # _____

_____ # _____

_____ # _____

B:

Characteristic	**Specification**	**Test Methodology** (SOP # or Other Standard)
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

10. Master formulae

The instructions for the manufacturing method are also written procedures but are not called SOPs. The full procedure is detailed in a Master Formula which details the preparations to be made, the equipment to be used, and the method to be followed. GMP documents from WHO and other countries all require that a Master Formula be prepared and approved for each batch size of every product manufactured. The Master Formula describes in detail all the manufacturing instructions for that specific batch of product.

The MF explains detailed step-by-step instructions for the production process: the details include the specific types and amounts of components and raw materials; the details of the processing parameters; indicates what in process quality controls are required; specifications for intermediates; environmental monitoring and control. The MF is written with blank spaces at each point where data or information is to be recorded to document that the production events occurred as directed. For some steps, the MF may refer to an SOP which describes a specific part of the production process.

In various GMP documents, the term for this master document differs slightly. WHO and Canada use the term “Master Formulae”; in the USA GMP Regulations the term is “Master Production and Control Record”; in the EU GMP guidelines the term is “Manufacturing Formulae and Processing Instructions”, and the Australian GMP Guidelines calls it “Master Formulae and Processing Instructions”. However, regardless of the term used, the information to be provided is essentially the same in each of these GMP documents.

The Master Formula (MF) is the document that explains the detailed steps included in a facility’s method for producing a batch of product. The MF can be prepared as a set of documents: one for each segment of the full production process (e.g. for the production of an intermediate such as a batch of harvest or for the formulation/filling process from final bulk), or a single overall document that contains parts which describe the separate batch products that make up the full process from the starting materials to the final vialed product. If the MFs are prepared for batches of intermediate products, there will be several documents which together describe the full production process for a particular product from beginning to end. If the MF describes the full process, then the parts of the MF will describe production process for an intermediate product..

The sections described in the MF should correspond to the chronological operations for the major manufacturing steps. It should have a first section with component preparation such as cleaning, equipment preparation, raw material preparation, etc. (It can be convenient to divide the sections up on a day-by-day basis). There must be

spaces provided for approval initials for each step as it is performed, and any deviations that may occur must be recorded at the time in the margins. Verification signatures or initials of another operator may be required for critical processes and space should be provided accordingly for these steps. Space for review by a supervisor must be included. All products, equipment and facility areas listed in the MF should have reference numbers associated with them to permit traceability.

The format for the MF should be a formal document with the company name, product name, batch size, site of manufacture, a document number with revision number, and approval signatures and dates. Each page should be numbered and spaces should be provided to fill in the lot number of the batch and for approval signatures.

The MF, and any revisions, must be approved, with dated signatures, by both Production and QA officials. The original should be filed in a safe place and approved copies are made for each production run. The lot number of the batch is filled in on each page, and approval signatures and information are filled in as required and distributed for use for each production order.

An SOP describing the writing, approval, distribution and use of the MF should be prepared.

An example of a Master Formula for a hypothetical biological product is found in Appendix 6.

Batch Processing Records

A batch processing record is built up by filling in all the blanks on an approved Master Formulae sheets. An approved copy of the MF is requested by the production department for each production run of a batch. The Batch Processing Record Document must be verified by QA or QC as an exact replica of the current MF before being released for a batch production run. It is ideal to have the batch processing record divided by day (see format in later section of this guide) so that only the required blank pages of the batch processing record are taken into the production area for each day of a production run.

Batch

Batches are defined as a specific quantity of a drug or material that is produced in a single manufacturing operation having a uniform character and quality and which meets predetermined specifications. Depending on the production method of the material being manufactured, a batch can be the result of a continuous production process of a drug, or a defined part of the production process. For example, a batch can be the production of a crude harvest of a bacterial or viral vaccine from a fermentation run; or it can be a bulk purified product manufactured from raw materials or from crude harvest; or it can be the formulation and filling of a bulk into the final container product. In each of these examples, the “batch” is the product of a process with a defined starting and ending point, and usually with a storage period at both beginning and end. Each of these separate production events would have a separate batch record documenting the procedures and process parameters carried out.

Batch Processing Record Review

A product record, is assembled from the batch processing records, lyophilization record, environmental monitoring records, inspection reports, sterilization records, quality control records, etc. The final release of the product can only occur when the entire product record has been reviewed and approved by a Production Manager and QC and QA departments according to an SOP for Batch Processing Record Review and Approval.

Format for a Master Formula

Cover Page

Name of Facility *ABC Vaccine Manufacturing Company* **page** *1* **of** *8*

Master Formula: *Doc # 888* Revision number *2*

Product Name _____ Product Code _____ Batch Size _____

Written by _____ Edited by _____

Production Approval Signature _____ Date _____

Authorization Signature _____ Department (QA/QC) _____ Date _____

Effective date_____ Replaces *Rev 1* .

MF Doc: *888* **Rev** *2* **Name of facility** *ABC Vaccine Manuf Co.* **page** *2* **of** *8*
Product name: _____ **Code #**_____

Part 1: Fermentation

Batch size _____ Fermentation Lot No. _____

Theoretical Yield _____

Date Started: _____ Operators _____

_____

Date Finished: _____ _____

_____

Day 1: Preparation:

This section should list all the preparative work and checks which are required before beginning the procedure. A checklist for: facility preparation; production location; equipment preparation; reagent preparation; and for preparation and entry of incoming supplies needed for the days operations is found in this section of the record. The checklist should give reference to the SOP numbers followed during the preparation, expiry dates of reagents where applicable, QC approval dates for starting materials, raw materials, supplies and reagents, and dates of cleaning and calibration of equipment.

Day 1: Manufacturing Instructions

This section contains the step by step instructions for the process performed on Day 1 in sequential order. There should be blanks for all information and data to be entered and spaces for signatures, initials and dates. All steps including sampling for QC tests should be indicated. Many operations will be recorded by checking a box to indicate the step was performed. Timed operations should have a space to fill in the beginning time and the finishing time. Weighings should have a space to record the tared weight and final weight. Any calculations should be presented as a formula with blanks to fill in. All critical steps and blanks for times and weights and all calculations should have an additional blank space for the initials of second operator who verifies the reading or calculation. If an item of measuring equipment has a printed readout, the verification signature is not necessary, but the printout must be attached to the record as well as the value entered in the appropriate blank on the record.

Day 1: Cleanup

A checklist of the step-by-step instructions for the procedure for cleaning up after the days production is completed including: waste disposal, removal of reagents, storage of intermediates if appropriate, status of equipment, cleaning procedures performed before leaving. Blanks and checkboxes and spaces for signatures, initials and dates are on the checklist.

Day 1: Reporting

The days record is delivered to the Production manager at the end of the day.
The Production Manager reviews and signs each page of the record.

Part 1: Fermentation, continued **Date:** _____ **Lot #** _____

Day 2: Preparation

Preparation information for the steps for the continuation of the fermentation process performed on the second day are to be provided in a checklist with all the appropriate information (see day 1).

Supplies and reagents brought in for day 2, and any calibrations, cleaning or preparation of equipment done on day 2 must be entered on the checklist.

Day 2: Manufacturing Instructions

Continued step-by-step instructions for all the steps of the process performed on day 2, blanks and checkboxes for entering data, and spaces for signatures, initials and dates.

Day 2: Cleanup

A checklist of the step-by-step instructions for the procedure for cleaning up after the days production is completed including: waste disposal, removal of reagents, storage of intermediates if appropriate, status of equipment, cleaning procedures performed before leaving Blanks and checkboxes and spaces for signatures, initials and dates are on the checklist.

Day 2: Reporting

The day's record is delivered to the Production Manager at the end of the day.

The Production Manager reviews and signs each page of the record in the appropriate blanks.

This format continues for the full number of days for this fermentation part of the production process. The batch for fermentation will end with the storage of the single or pooled harvests, depending on the manufacturing process.

MF Doc: *888* Rev *2* Name of facility *ABC Vaccine Manuf Co.* page *4* of *8* Product name: _____ Code #_____
Part 1: Fermentation, continued **Date:** _____ **Lot #** _____
Day X: Preparation Preparation information for the steps for the continuation of the fermentation process performed on the last day are to be provided. Supplies and reagents brought in for the last day, and any calibrations, cleaning or preparation of equipment done on the last day must be entered on a checklist.
Day X: Manufacturing Instructions Similar step-by-step instructions for the procedure for the final day's processing, blanks and checkboxes for entering data, and spaces for signatures, initials and dates. The final step will be the sampling of the batch to send to the QC department for testing and the instructions for labelling and quarantine storage of the finished fermentation batch (single or pooled harvests).
Day X: Cleanup A checklist of the step-by-step instructions for the procedure for cleaning up after the days production is completed including waste disposal, removal of reagents, storage of intermediates if appropriate, status of equipment, cleaning procedures performed before leaving. There should be blanks and checkboxes for entering data, and spaces for signatures, initials and dates.
Day X: Reporting The day's record is delivered to the Production Manager at the end of the day. The Production Manager reviews and signs each page of the record.

The above pages should be formatted so that each day's instructions begin on a new page. This will limit the number of pages to be taken into the production area each day.

The detailed manufacturing steps for the batch of harvest will finish with the completion of the batch processing records filled out in the production area. However, these will be followed by a review of the production process and a review of the yields, QC test results, and QC or QA review and approval of the batch records and release of the product from quarantine to release storage as an approved starting material for the next part of the production process.

Part 2: Purification Process

Batch size: _____ Purified Bulk Lot No. _____

Theoretical Yield: _____

Harvest lots used: _____

Date Started: _____ Operators _____

_____

Date Finished: _____ _____

_____

The same type of day-by-day instructions for the preparation, step-by-step procedure, and cleanup is prepared for the purification process - from harvest to purified bulk.

The single or bulk harvests now become the starting material to be entered in the preparation lists for day 1 of purification.

The QC release of the of the harvest(s) is required before beginning this part of production. There should be a space to enter the date of production and the date of QC approval in the preparation section of this record.

The final step will again be the sampling of the purified bulk to be sent to QC for testing and labelling and putting into quarantine storage.

This format continues for the full number of days for this purification part of the production process.

The batch for purification will end with the storage the purified bulk.

The production steps will be followed by a review of the production process and a review of the yields, QC test results, and QC or QA review and approval of the batch records and release of the product from quarantine to release storage as an approved starting material for the next part of the production process.

MF Doc: *888* **Rev** *2* **Name of facility** *ABC Vaccine Manuf Co.* **page** *6* **of** *8*
Product name: _____ **Code #**_____

Part 3: Final Bulk Formulation

Batch size: _____ Purified Bulk Lot No. _____

Theoretical Yield: _____

Harvest lots used: _____

Date Started: _____ Operators_____

_____

Date Finished: _____ _____

_____

Again, the same type of day-by-day instructions for the preparation, step-by-step procedure, and cleanup is prepared for the purification process - from purified bulk to the final formulated bulk.

The purified bulk is the starting material to be entered in the preparation lists for day 1 of formulation.

The QC release of the of the purified bulk is required before beginning this part of production. There should be a space to enter the date of production and the date of QC approval in the preparation section of this record.

The final step of this part of the production process will again be the sampling of the final formulated bulk to be sent to QC for testing and labelling and putting into quarantine storage.

This format continues for the full number of days for this formulation part of the production process.

The batch for formulation will end with the storage the final formulated bulk.

The production steps will be followed by a review of the production process and a review of the yields, QC test results, and QC or QA review and approval of the batch records and release of the product from quarantine to release storage as an approved starting material for the next part of the production process.

MF Doc: *888* **Rev** *2* **Name of facility** *ABC Vaccine Manuf Co.* **page** *7* **of** *8*
Product name: _____ **Code #**_____

Part 4: **Filling/Lyophilization/Sealing of Ampoules** *or*
Filling/Lyophilization of Vials *or*
Filling/Stoppering/Capping of Vials (liquid product) *and*
Inspection

Batch size: _____ Final Lot No. _____

Theoretical Yield: _____

Final Bulk Lot: _____

Date Started: _____ Operators _____

_____

Date Finished: _____ _____

_____

Again, the same type of day-by-day instructions for the preparation, step-by-step procedure, and cleanup is prepared for the purification process - from final formulated bulk to final filled container. Inspection of 100% of the vials should be performed and the numbers of vials rejected and the reasons for rejection should be recorded. The MF should contain a list of the defects to be looked for (cracks, particles, colour, turbidity, crooked stoppers, poor seals, etc).

The final formulated bulk is now the starting material to be entered in the preparation lists for day 1 of filling or filling/lyophilization.

The QC release of the of the final formulated bulk is required before beginning this part of production. There should be a space to enter the date of production and the date of QC approval in the preparation section of this record.

A filling order is prepared and delivered to the Filling Department to initiate this part of production.

This format continues for the full number of days for this filling or filling/lyophilization part of the production process.

The final step of this part of the production process will be the inspection of the final containers, applying quarantine stickers,transferring to quarantine storage, and advising QC that the fill is completed and ready for them to take samples for testing.

The production steps will be followed by a review of the production process and a review of the yields, QC test results, and QC or QA review and approval of the batch records and release of the product from quarantine to release storage as an approved starting material for the next part of the production process.

MF Doc: *888* **Rev** *2* **Name of facility** *ABC Vaccine Manuf Co.* **page** *8* **of** *8*
Product name: _____ **Code #**_____

Part 5: Labelling and Packaging

Batch size: _____ Final Lot No. _____

Date Started: _____ Operators _____

_____

Date Finished: _____ _____

_____

Again, the same type of instructions for the preparation, step-by-step procedure, and cleanups prepared for the labelling and packaging process - from unlabelled final container to the labelled/packaged final container.

The final unlabelled containers are the starting materials to be entered in the preparation lists for day 1 of labelling.

The QC release of the of the unlabelled filled lot is required before beginning this part of production. There should be a space to enter the date of QC approval in the preparation section of this record.

The final step of this part of the production process will be the sampling of the final labelled vials to be sent to QC for identity testing, and putting into quarantine storage until released by QC.

A labelling order is prepared and delivered to the Labelling/Packaging department to initiate this part of production.

The batch for labelling/packaging ends with the quarantine storage of the final labelled containers.

The production steps will be followed by a review of the production process and a review of the yields, QC test results, and QC or QA review and approval of the batch records and release of the product from quarantine to release storage for shipment.

11. Priorities for the preparation of SOPs and master formulae

The WHO Guidelines for Good Manufacturing Practice (ref. 21, 27) and all other national and international GMP Regulations and Guidelines (ref. 3, 5, 7, 11, 18, 19) clearly indicate that written procedures must be established and followed to be in compliance with GMP. The term "written" occurs many times and covers all production, control, and administrative operations.

Each manufacturer should evaluate the present status of their documentation system and prepare a list of SOPs, forms and other documents needed to meet WHO GMP requirements. If many documents are to be written, it is most productive if the staff performing the procedure writes the initial draft, another operator or the supervisor reviews and revises it, and the department head accepts the final version. The staff performing the procedure usually know it the best, and it also is easier for a supervisor to revise several SOPs than prepare them. Signatures of the personnel from QC or QA department, as appropriate, must be obtained for final approval. An SOP for the review and approval of SOPs for each department should be one of the first administrative procedures to be developed.

In most cases, it is fairly easy to prepare the written procedure for the QC testing of raw materials, in-process intermediates and final product for traditional vaccines currently in production. Most of these tests are well described in WHO technical reports (ref 24-26) and manuals (ref. 22, 23, 28-31). Many chemical and biochemical assays are available in Pharmacopoeia, in Chemical Society Standards, and others and are internationally recognized standardized methods. Each of these assays can be printed in the format presented in this guide, or in another suitable format adopted by the manufacturer. These standard procedures should be put into the manufacturer's formal SOP format.

It should also be straightforward to prepare Master Formulae for the manufacturing instructions for manufacturers' current vaccines. The steps of the production process, the equipment and materials used, and the time-frames should be well defined.

SOPs for equipment operation, maintenance, and calibration can also be put in written form fairly quickly because very often the equipment manuals provide the detailed information needed.

However, the requirement for written procedures is not limited to the production method, equipment operation and test methods. The more difficult SOPs to prepare are those describing control of materials at every stage, monitoring of storage conditions, requirements for storage segregation, SOPs for gowning, cleaning, fumigating the facility, monitoring equipment, monitoring the facility air and surfaces, SOPs for

entry of materials in and out of the clean and aseptic areas, SOPs for personnel health and hygiene, animal care SOPs (raising, feeding, treating, health, cleaning and maintenance of animal facilities, cage washing, quarantine of animals, etc.), SOPs for testing cell, viral and bacterial characteristics, SOP for egg candling, SOPs for self-inspections and audits, SOPs for sampling, and even an SOP for writing, revising SOPs, and one for controlling the distribution of all the other SOPs. (Forms for recording the data or information obtained during the course of carrying out these procedures must be generated for each SOP, as appropriate, to ensure accurate records).

All of these procedures have an impact on the quality of the product because each is concerned with the quality of the incoming materials, with the operating conditions and cleanliness of premises and equipment used, and with the animals, or biological materials used to produce or test the product.

Three Vaccine Manufacturers have contributed a list of the titles of their SOPs. The lists are in Appendix 2 and can be used as a reference for assessing the SOPs needed for a vaccine production facility.

Appendix 1: List of document requirements

Standard Operating Procedures

Raw Materials	Specifications/Product Codes Supplier Approval Receipt and Storage Sampling Procedures QC Testing, Inspection, Quarantine, Release and Approval
Biological Starting Materials (e.g. Cells, Eggs, Animals, Virus, Bacteria)	Specifications Source, Name, Characteristics, History Seed Lot System and Storage Tests before use in Production Supplier (Approval, Ordering, etc.) Animal Care Animal protocol review
Facility	Systems Operation, Maintenance and Calibration (e.g. HVAC*, water, clean steam) Cleaning of Facility Environmental Monitoring Entry and Exit to Cleanrooms Gowning Product Flow Supply Flow Staff Flow Air Flow Waste Flow and Disposal Garment Cleaning and Sterilization Glassware Cleaning and Sterilization Disinfectant/Fumigation Pest Control
Equipment (Production and QC)	Operation Cleaning/Sterilization (Surface, CIP, SIP, COP)* Preparation of Cleaning Solutions Residual Product and Cleaning Agents Preventive Maintenance Calibration Monitoring Calibration of Certified NIST Instruments

* HVAC = heating, ventilation, air-conditioning; CIP = Clean-in-Place; SIP = Sterilize-in-Place; COP = Clean-out-of-Place

Production	Master Formulae In-Process Tests (Production) Preparation of Process Buffers and Solutions Environmental Sampling
Labelling and Packaging	Label and Package Review and Control Specifications Reconciliation of Labels Expiration Dates
Quality Control	Testing and Release of Final Product Testing and Release of Intermediate/Bulk Product Analytical Assays Samples: Test and Retention Summary Protocol of QC Results Stability Studies Reference Standard and Control (Maintenance and Testing) Recertification/Recalibration of QC Equipment Preparation of Reagents and Materials for QC Tests
Quality Assurance	Batch Record Review Inspection/Internal Audits Validation Protocol Approvals Product Recall Product Complaints Contractor Audit Vendor Audit Document Control, Revision, and Distribution (Change Control) Employee Records, Health Records Training (Technical and GMP) SOP Writing and Approvals Adverse Event Reports Change Control Storage Temperature Monitoring Product Distribution Procedures Distribution Records Quarantine, Release, Rejection and Storage Master Validation Plan

Appendix 2: List of SOP titles from three vaccine manufacturers

The SOP titles listed on the following pages have been contributed by the collaborators on this project. These lists have been reproduced as an Appendix to this Guide to SOPs to provide examples of the number and diversity of SOPs needed for vaccine production and testing. They are listed in the order given by the contributor.

Massachusetts Public Health Biologic Laboratories, Jamaica Plain, Massachusetts

SOPs related to DTP Vaccine

SOP Title

Card Identification of Animals Released from Test
Control & Documentation of Veterinary Drugs for Animal Quarters
Annual Review of Animal Facility SOP's
Final Review of Adverse Reactions by Lot
Obtaining a Recall Distribution Mailing List and Labels
Generating Weekly Vaccine Distribution Reports
Generating Weekly Report by Product and Lot
Receiving and Logging of Vendor Supplied Product
Inventory of Products
Generating a Lot Reconciliation Report
Generating Biologic Monthly Distribution Reports
Generating Monthly Distribution Bar Chart
Procedure for Using Three-Part Maintenance Forms
Repair Logs for Refrigeration and Air Conditioning Units
Documentation Requirements for Fractionation Renovation
Documentation of a Standard Operating Procedure
Supervisory Review of Standard Operating Procedures
Initiation of Filling Numbers
Initiation of Lot History Records
SOP and In-process Form Change Control
Standard Operating Procedure and In-Process Form Computerized Document Storage
SOP for Document Changes
Preparing Documents for Typing
Method for Correcting Entries on all Records
Annual Review of Standard Operating Procedures
Reporting Problems with Vendors
Reporting of Production Incidents / Deviations & Resulting Actions
Annual Review of SOP's and In-Process Forms
Using the WordPerfect Macro / Template
Using the Lotus Template for In-Process Forms
Annual review of QA Documentation

Product Recalls
Product Complaints
Preparation of Biologic Laboratory Investigation Reports
QA Batch Record Review
Change Control
Data Analysis of VAERS Updates
Issuing Documents for Reference Manuals
Review and Acceptance of SOP's from Contract Organizations
Maintenance of B. Pertussis Cultures
Lyophilization of Pertussis Cultures
Growing Challenge Culture for the Pertussis Potency Test
Preparation of 10% Aluminum Chloride Solution
Preparation of High Phosphate Buffer (HPB)
Preparation of 5N Acetic Acid Solution
Preparation of 1.12 M Phosphate Concentrate Solution
Preparation of ALCL3 and Sodium Trihydrate Solution
Preparation of 0.29M Na3PO4-12H2O Solution
Preparation of Tryptic Soy Broth
Media Preparation for the Production of Diphtheria Toxin
Certification of Reagents Used in the Diphtheria Production Medium
Preparation of Wadsworth Broth
Preparation of 1% Peptone Solution
Preparation of Accessory Metal Solution
Siliconing of Vial Trays
Calculation of Aseptic Filling Yields
Determination of Tetanus Culture Purity: Production Lots
Production of Pertussis vaccine
Filtration of Dow Silicone 365 Emulsion
Tetanus Filtration
Filtration of Crude tetanus Toxin
Sterilization of the 13mm and 20mm Flange and Split Vial Stoppers
Depyrogenation of Vials Using the Despatch Dry heat Oven
Set-Up and Sterilization of a Single DUS-10 Syringe
Detoxification of Tetanus Toxin
Decontamination of Used Equipment & Glassware in Tetanus Production
Determination of Optimal Concentration of Ammonium Sulfate for Toxoid or Toxin Purification
Final Component Diphtheria or Tetanus Toxoid Pools
Purification of Diphtheria Toxoid - Ammonium Sulfate Method
Purification of Diphtheria Toxoid by the Batch Column Method, Using Sephadex DEAE A-50
Intradermal Toxicity Test for Detoxification of Diphtheria Toxin
Tetanus Toxicity Test per Minimum Requirements
MLD Determination of Tetanus Toxin from Production lots
Test for Reversed Tetanus Toxoid
Diphtheria Toxoid Reversion Test
Passivation Records and Testing of Welds in newly Installed Systems
Filter Integrity Test and Sterilization
Visual Inspection of Final Vial Rejects by QA
Floor Cleaning (Animal Rooms and Corridors)
Weekly Cleaning of Animal Rooms
Cleaning of the Hall Walls
Changing of the Tacky mats in the Animal facility
Weekly Inspection of the Animal Facility
Drain Cleaning

Restrictions in a Class 2 Containment Room
Working in a Level 2 Containment Room in the Animal Quarters
Restrictions in the Animal Quarters Area
Floor Patching in Animal Quarters
Collection, Autoclaving and Packaging of Sharps Containers
Disinfectant Change Method
Gowning for Aseptic Filling Operations
Gowning Requirements within the Filling and Distribution Department
Preparing the Aseptic Fill Area for Janitorial Cleaning
Cleaning of the Filling Area BG-34 by the Janitorial Staff
Gowning for Aseptic Vaccine Formulation Operators
Cleaning Procedure for Compositing Area
Calibration of Cage Washer Thermocouples
Calibration of Hydrometers
Calibration of Sanitary Gauges
Calibration of RCS (Biotest) Viable Air Sampler
Annual Standardization of Diphtheria Flocculating Antitoxin
Necropsy / Sampling Procedure for Moribund or Dead Animals
Procedure for Aseptic, Survival Surgery in Rodents
Cardiac Puncture in Guinea Pigs
Obtaining Blood Samples from Mice via Tail Nicks
I.P. (intraperitoneal) injections of Guinea Pigs
Drug Procurement in the Animal Quarters
I.M. (intramuscular) injections of Mice, Guinea Pigs, and Rabbits
Retro-Orbital Bleeding of mice with Anesthesia
Cardiac Puncture in Rabbits
Retro-Orbital Bleeding in Mice
Cardiac Puncture in Mice
Procedure for Ordering Animals
Entering Computer Generated Orders for Shipping Biologic Products
Printing Packing Slips and Mailing Labels for Computerized Orders
Procedure to follow when bitten by a Laboratory Animal
Off-Hour Notification of High/Low Temperature Alarms
Protocol Certification in Animal Quarters
Monitoring of GMP Training for the MPHBL
Training program for MPHBL Staff
Operator certification for SOP's
CFR Readings for Biologic Lab Staff
Training Program for Compositing Procedures
Disposition of Returned Product
Control Testing of Liquid Media Used with Milliflex System
Preventive Maintenance, Ingersoll-Rand Air Compressor
Preventive Maintenance, Sullair Air Compressor
Preventive Maintenance, Van-Air Dryers
Preventive Maintenance and Maintenance of Autoclaves
Preventive Maintenance Animal Quarters Filtration System
Operation & Maintenance for the HVAC and Cold Rooms
PM Compressed Air Systems - Kaeser
Preventive Maintenance Program
Changing Tubing at WFI Ports - Filling
Monitoring Cold Rooms - Filling
Shipping/Receipt of Bulk Product Tanks
Monitoring of Equipment, Diphtheria Section
Cleaning & Set-Up of Equip. in Sterile Fill Area (Rm. BG-34) Before a Fill
Initial Set-Up and Operation of Metromatic Vial Washer

Preparation of Bulk Product Tanks for Aseptic Fillings
Identification of Major Equipment
Preparation of Tyvek Bags for Lyophilized Fills
Preparation of Goggles for Aseptic Fillings
Set-Up and Operation of Ultrafiltration System
Preparation of Rubber Stoppers
Compositing Preparations and Arrangement
Assembly of Tanks Used in Vaccine Formulation and Bulk to Fill
Preparation and Assembly of Transfer Apparatus (TA) / Siphons
Preparation and Assembly of Transfer Graduate Cylinder
Preparation of Gowning Packages for Vaccine Compositing
Set-Up & Operation of the HIAC/ROYCO Particle Counter Model 5250
Operation of Filling Autoclave
Turbomatic 3000 Operation for Cleaning Glassware
Use of Jouan KR22i High Speed Refrigerated Centrifuge
Operation of the Sorvall (Toxoid Purification) Centrifuge
Operation of the BioTest RCS Air Sampler
Cleaning Procedure for Mouse Cages
Cleaning Procedure for Guinea Pig and rabbit Cages and Pans
Cage Washing Procedure for Laboratory Animal Cages
Cleaning Procedure for Cage Racks
Incinerator Cleaning
Acid Cleaning Procedure for Stainless Steel Pans
Calibrating Balances in the Animal Quarters
Cleaning Procedure for Cage Washer
Cage Washer Operation
Procedure for Cleaning the Bedding Disposal Hood
Cleaning of Dus Syringes and Chase Filling Machine (M-3) Parts
Cleaning of Vials the Metromatic Vial Washer
Routine Calibration of Fairbanks-Morse Scale (Serial #6269896)
Calibration of OHAUS Brainweigh B3000D
Nomenclature of Diphtheria Toxins and Toxoids
Cleaning Procedures for Filter Holders & Pressure Pots
Laboratory Tests -- Diphtheria Production
Tryptic Soy Agar Slit Sampler Plate Preparation
SOP's and In-Process Forms: Organization and Distribution
Sending Products for Concurrent Testing
Bulk sampling Certification / Masterfile Creation
Guidelines for Document Preparation
General Safety test
Sterility Testing Using Direct Inoculation
Number of Final Vials Needed for QC Testing and Reserves
Responsibilities of the QC Unit
Sterility Testing Using Membrane Filtration
Thimerosal determination
Personnel Training in QC
Elements of a Successful Training Program
Control Testing of Thioglycollate Broth and Tryptic Soy Broth for Sterility Testing via Membrane Filtration
Gowning Requirements for Sterility Room (BG9A) Operations
Sample Distribution of Final Vial, Bulk, and Stability Samples
Annual Review of SOP's
Purity Check of Biological Indicators
Final Vial Visual Inspection of Vaccines
Growth-promoting Ability of Broth Used in Sterility Testing Using the Steritest System or Direct Membrane Filtration

Growth-Promoting Ability of Broth Used in Sterility Testing using Direct Inoculation
Growth-Promoting Ability of Commercial Broth Used in Sterility Testing Using the Direct Inoculation (Sealed Containers)
Fluid Thioglycollate Broth Preparation (for Sterility Testing)
Tryptic Soy broth (For Sterility Testing)
Labelling Procedure for Quarantined and Released Products and Procedure for Release for Distribution
Date of Manufacture, Dating Period, Storage Period for Blood Products and Vaccines
Final Container product Reserve Samples
Detection and Quantitation of Residual Tetranitromethane in Pertussis Toxoids
DTP Pertussis Potency Computer Program
Use and Function of the IEC Centra-W Cell Washer
Use and Function of the Dade Automatic Centrifuge II (DAC II)
Operation of the Milliflex-100 System
NIST Equipment
Test for Potency of Precipitated or Adsorbed Tetanus Toxoid (DTP, DT, Td, and T)
Test for Potency of Precipitated or Adsorbed Diphtheria Toxoid (DTP, DT, TD, and the AK component of Td)
Procedure for the Potency Test of Pertussis Vaccine
The Lf Test for Diphtheria Toxoid in Tetanus and Diphtheria Toxoids for Adult use
Mouse Toxicity Test of DTP
Nitrogen Determination of Vaccine Components Using the Bradford assay
Validation of Cleaning processes Using Swabs
Nephelometry Measurement by use of the Hach Turbidimeter
Test for Residual Formalin in Toxoid Preparation
Pararosaniline Method for the Determination of Free Formaldehyde in Vaccines
Identity Testing of Biologic Products
Optical Transmission Check for the DTP vaccine
Determination of the Residual Sodium Cholate Content in the Acellular Bordetella Pertussis Toxoids
Preparation Procedure for Compositing
Stability Program for all MPHBL products
Stability Testing of Bacterial Vaccines
Preparation and Scheduling of the Cleaning / Disinfecting Solutions
Schedule for the Cleaning and Monitoring of the Sterility Room (BG9A)
Procedure for Thermometer Certification
Evaluation of New Cleaning Agents
QC personnel Monitoring
Calibration of Cliniscan II Densitometer
Certification of Pipettes
Silicate Testing
Quarterly Microbial Monitoring of City water
Annual Environmental Monitoring for Viable Organisms in production areas of the Biologic Laboratories
Water Quality Tests
Microbial Monitoring of Environment During the Filling Process
Use of Microbial Monitoring Plates in the Compositing environment
Quarterly Calibration of Cold Rooms, Incubators, and water Baths
Quarantine and Release of a Bulk Product (Blood Product, Bacterial Vaccine, Placebo medium)
Usage of the QC Requisition Form for Testing
Reagents Used in Preparation of Diphtheria Toxin medium
Calibration of Pressure Gauges
Prep of 20% Cysteine Solution
Monitoring of UV Germicidal Lights
Waters High Performance Liquid Chromatograph Model 840

Ohaus Galaxy Model 160
Ohaus Model B1500 D
Mettler Model AE 200 & 50 - Calibration and Operation
QC Testing of Trypticase Soy Broth Medium for Broth Fills Validation
Calibration procedure for the Gas Chromatograph Perkins Elmer 8310
Calibration of the Hitachi U-2000 Spectrophotometer
Testing of Incoming Materials: Vials, seals, and Stoppers
Testing of Incoming Materials: Venusa IV Sets (Red Cross)
Testing of Miscellaneous Incoming Materials: Gaskets, Connectors, O-Rings, etc.
Control Testing of 0.1% Peptone Used in Sterility Testing (RQC of Peptone)
Testing of Incoming Materials: bags, Pyrogen-Free Tubes, Celite (SuperCel)
Testing of Incoming materials: Tubing
Control Testing of Rodac Plates, Settling Plates, TSA Plates, and RCS Strips
Control Testing of Reagents
Control Testing of 0.1% Peptone Used in Sterility testing
Purity Check with the use of HPLC for Niacin, Vitamin B1, Vitamin B6, and Uracil
Acetic Acid
Identity Test for Boric Acid
Identity Test for Bromocresol Green
Calcium Chloride
Calcium pantothenate
Casamino Acid (technical)
N-Z Case, certified Casamino Acids
Identity Test for Citric Acid
Identity Test for Crystal Violet
Identity Test for Cupric Sulfate
Cyanocobalamin
Identity Test Ammonium Oxalate
ID / Purity Testing of B Cyclodextrin
L-Cysteine
Cysteine
Identity Test for DEAE-SEPHADEX (anion exchanger)
Dextrose
ID / Purity Test for Dithiothreitol
Identity / Purity Tests for Ethanolamine
Ferric Chloride
Identity Test of N-Acetyl DL Trytophan with the use of UV Spectrophotometry
Ferrous Sulfate ID
Formaldehyde Identification
Identity test for Fetuin
Identity / Purity test of Glutamic Acid
Identity / Purity Tests of Monosodium Glutamate
Identity of Glutathione
Glycerin Identification
Identity Test for Glycine
Hydrochloric Acid
Iodine
Identity of Kanamycin Sulfate
Manganese Chloride
Identity Test for Agar
Magnesium Sulfate
Maltose
Magnesium Chloride
Identity Test for Mercuric Sulfate
Identity Test for Methyl Red
Nonfat Dry Milk - Carnation

Niacin
Phenol Identification
Pimelic Acid Identification
Potassium Chloride identification
Identity Test for Aluminum Chloride
Potassium Iodide
Potassium Phosphate, Dibasic Identification
Potassium Phosphate, Monobasic Identification
Identity Test for Potassium Sulfate
Identity Test for Potassium Thiocyanate
Identity / Purity Tests of proline
Proteose Peptone Identification
Pyridoxine Hydrochloride Identification
Identity Testing of Riboflavin
Silver Nitrate
B Alanine
Identity Test of Safranin-o
Identity Testing for Dow Corning 365 silicone
Sodium Acetate Identification
Sodium Bicarbonate
Sodium Borate
Identity Test for Sodium Carbonate
Identity testing for Sodium Caprylate
Sodium Cholate
Sodium Chloride
ID Test for Sodium Hydroxide
Identity Test for Aluminum Sulfate
Sodium Lactate
Sodium Phosphate Dibasic Anhydrous
Sodium Phosphate Monobasic Monohydrate
Sodium Phosphate Tribasic 12-hydrate
ID Test for Sodium Thiosulfate
Starch
Sucrose
ID / Purity Test for Tetranitromethane (TNM)
Identity Thiamine Hydrochloride
Thimerosal
Identity Test for Sulfuric Acid
Identity Test for Barium Chloride
Thioglycolic Acid
ID / Purity of Tris (Hydroxymethyl) Aminomethane
Uracil
Identity Test of yeast extract
Zinc Sulfate
Identity Test of Phosphoric Acid
ID Test of the Antifoam Reagent
ID Testing of Ascorbic Acid
ID / Purity Tests for Chloroform (CHC13)
ID Test and Purity Determination for Urea
Identity Test for Biotin
ID of (Acid Sanitizer) Phosphoric Acid
ID of Caustic Chlorinated CIP Chemical
Cyanogen Bromide
Potassium Hydroxide identification
Identity Test for Actigel-ALD Superflow and Coupling Solutions
Identity Testing of Sepharose

Sodium Cyanoborohydrite
Sodium Phosphate Dibasic 7 Hydrate
Purity & Specific Gravity determinations for 95% Ethanol
Operating the FTIR Model 1620 for Chemical ID and Purity Check
QC Testing of Incoming Component Raw Materials
Testing of Incoming Materials: Filters
Testing of Incoming materials: Tucks, Circulars, and Labels
Filtration of formalized tetanus Toxin
Tetanus Toxin / Toxoid production : Flow Chart
Tetanus Toxin / Toxoid Production: Flow Chart
Centrifugation of Samples
Certification of Toxin Producing Ability of Casein Digests
Calcium determinations of Casein Digests Used for Tetanus
Glassware Cleaning and Validation of Cleaning
Bacterial Monitoring of tetanus BSC's
Calibration of Ohaus 4000D Toploading Balance
Use and Calibration of Orion #501 pH Meter
Monitoring of Incubator, Cold Room, Freezer, and Refrigerator Functions
Standardization of Thermometers

Biomanguinos/FIOCRUZ, Yellow Fever Vaccine Production Facility, Brazil

SOPs related to producing vaccine against yellow fever

List A:

Autoclave operation
Autoclave control using biological indicators
Biosafety sign standardization
Clothes washing machine operation
Coloration verification of vaccine against yellow fever
Control and filing of diluent and vaccine protocols
Control and filing of equipment and instrument manuals
Daily temperature control
Eggs type SPF transillumination
Eggs type SPF selection
Eggs type SPF incubation
Elaboration and application of Defective Fraction Control Charts
Embryonic pulp freezing and storage
Embryonic pulp thawing
Filling process of vaccine against yellow fever
Fine balance calibration
Fine balance operation
Furnishment of animals, animal derived products and raw materials
Guidelines related to personnel access to the facilities of Bio-manguinhos
Guidelines for requisition of imported materials
Handling and storage of materials
Hot air oven operation
Humidity control
Inoculation in eggs type SPF
Internal audits preparation and execution
Labelling of references used in SOPs
Material reception
Max-min. thermometer verification
Non-conformity report and corrective action
Particle counter and air velocity measurements in Laminar Flow Units
pH determination of vaccine against yellow fever
pH meters calibration
Filling machine operation
Post-inoculation embryos collecting and embryonic pulp preparation
Preparation of material to be sterilized in autoclaves
Preparation of material to be sterilized in hot air ovens
Pressure gauge calibration
Product codification
Reference standards calibration plan
Residual humidity determination of vaccine against yellow fever
Room cleaning and disinfecting standardization
RTD Thermometer operation
Specification for specific pathogen free animal facilities
Specification for vaccine against yellow fever
Specification of diluent of vaccine against yellow fever
Sterilization process execution in autoclave
Sterilization process execution in hot air oven
SOPs elaboration process and format
SOPs verification, approval and releasing of revised version

SOPs codification system
SOPs control
Suppliers rating and qualification audits
Uniform standardization
Use and control of labels devoted to indicate calibration stage of instruments
Visual inspection of vaccine against yellow fever
Water purification system monitoring process

List B:

Ammonia determination of diluent of vaccine against yellow fever and measles
Archive storage of produced immunobiologics
Aspiration of embryonic pulp
Aspiration of viral suspension
Autoclave operation
Automatic packaging line operation
Butyl rubber stopper specification
Centrifugation of embryonic pulp
Chloride determination of diluent of vaccine against yellow fever and measles
Closing of vaccine against yellow fever
Collecting of distilled water sample to be sent to chemical control
Conductibility determination of diluent of five-dose vaccine against yellow fever and measles
Culture media sterilization process
Dispatch of vaccine against yellow fever
Formulation of vaccine against yellow fever
Filling of vaccine against yellow fever
Freeze-drying of vaccine against yellow fever
Glass vial specification for parenterals
Identity test of vaccine against yellow fever
Infected material sterilization process
Inoculation purpose material sterilization process
Label printer machine operation
Manual packaging line operation
Mean volume determination of diluent of vaccine against yellow fever and measles
Mean weight determination of vaccine against yellow fever
Needles maintenance
Oven operation
Packaged immunobiologic storage
Packaging material preparation and control
pH determination of diluent of vaccine against yellow fever and measles
Potency determination of embryonic pulp of vaccine against yellow fever
Potency determination of vaccine against yellow fever
Preparation of Beaker to be used in disinfecting of aseptic area
Preparation of disinfectant to be used in aseptic area
Preparation of 70% diluted alcohol to be used in aseptic area
Preparation of Formalin solution fumigation
Preparation of glass protector for needles
Preparation of material for collecting purpose
Preparation of material for inoculation purpose
Preparation of material to be used in vaccines
Preparation of plastic stopper cover for 1.000 mL bottles
Preparation of rubber stopper cover for 1.000 mL bottles
Preparation of stoppers for culture media tubes
Preparation of stoppers for Erlenmeyer
Preparation of stoppers for Measuring Cylinders
Preparation of sulphochromic solution
Preparation of iodinated alcohol solution

Production process of diluent of vaccine against yellow fever
Preparation and execution of internal audits
Reception and storage of immunobiologics to be packaged
Reception, inspection and labelling of material in storage area
Report and corrective action of non-conformities found in receipt or final products
Sampling plans for receipt, in process and final inspection
Sending of released immunobiologic for dispatching
Siliconization of rubber stoppers to 3 mL vials
Sterilization process of materials to be used in collecting
Sterilization process of materials to be used in vaccine
Storage of vaccine against yellow fever
Thermostability determination of vaccine against yellow fever
Washing of rubber stoppers for 1.000 mL bottles
Washing of rubber stoppers for 3 mL vials
Washing process of material for incubating and collecting purposes and to be used in vaccine
Water distillation

Gerencia General de Biologicos y Reactivos, Mexico City, Mexico

SOP for DTP Vaccine

- Raw material sampling
- Raw material testing
- Cleaning and sanitization of clean rooms
- Washing of glass material
- Sterilization of glass material
- Preparation of culture medias
- Preparation and sterilization of clean clothes
- Preparation seed lot system
- Inoculation of fermentors
- Harvest of cultures
- Detoxification of cultures and toxins
- Separation of cells
- Purification of Toxoids
- Aseptic filtration of Toxoids
- Sampling products in process and final products
- Preparation of adjuvant
- Blending
- Filling, stoppering and sealing
- Inspection
- Labeling
- Sterilization in ovens and autoclaves

Quality control

Control of single harvests

- The bacterial grow rate opacity, pH and rate of toxin production
- Purity
- Purification

Control of bulk purified Toxoid

- Sterility
- Specific toxicity
- Reversion to toxicity
- Antigenic purity
- Formalin content

Control of final bulk

- Preservative content
- Adjuvant content
- Sterility
- Specific toxicity
- Potency
- pH

Control final product

- Identity
- Sterility
- Potency
- Innocuity
- Adjuvant content
- Preservative content
- pH
- Inspection
- Stability

Other

- Personal training
- Change control procedures
- Formats
- Reports
- Appendices

Appendix 3: List of reference articles and publications

(1) American Association for the Accreditation of Laboratory Animal Care. Outline for Description of Institutional Animal Care and Use Program, (with reference to Guide for the Care and Use of Laboratory Animals. DHHS Publication, Revised 1985), 1992

(2) Austin P.R., Design and Operation of Pharmaceutical Bio-cleanrooms and Aseptic Areas. Contamination Control Seminars, Michigan, 1994

(3) Australia. Therapeutic Goods Administration, Australian Code of Good Manufacturing Practice For Therapeutic Goods-Medicinal Products, August 1990

(4) Canada, Drugs Directorate Guidelines. Acceptable Methods. Health Protection Branch, Health Canada, 1994

(5) Canada, Drugs Directorate Guidelines. Good Manufacturing Practices (GMP) Guidelines, Consultation Draft Fourth Edition. Health Protection Branch, Health Canada, 1995

(6) Chapman K.G., Fields T.J., Smith B.C., "Q.C." Pharmaceutical Technology, January 1996, pp74-79

(7) Commission of the European Communities. Guide to Good Manufacturing Practice for Medicinal Products. The Rules Governing Medicinal Products in the European Community, Volume IV, Jan 1992

(8) Commission of the European Communities. Stability Tests on Active Ingredients and Finished Products (July 1988). Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use, The Rules Governing Medicinal Products in the European Community, Volume III, 1988

(9) DeSain C., Documentation Basics That Support Good Manufacturing Practices. Advanstar Communications, OH, 1993

(10) DeSain C., Standard Operating Procedures and Data Collection Forms, Documentation Basics, BioPharm, October 1991, pp 22-29

(11) Guideline for Good Manufacturing Practice in Egypt, Faculty of Pharmacy, Cairo University, Central Administration of Pharmacy, WHO, 1994

(12) IES. Microorganisms in Cleanrooms, Contamination Control Division Recommended Practice 023.1. IES-RP-CC023.1, Institute of Environmental Sciences

(13) IES. Testing Cleanrooms, Contamination Control Recommended Practice 006.2, IES-RP-CC006.2, Institute of Environmental Sciences

(14) International Organization for Standardization. Quality Systems: ISO 9000-1, ISO 9001, ISO 9002, ISO 9003, ISO 9004-1, Geneva, 1994

(15) Lanese J., A Model Standard Operating Procedure for Validation, The Documentation Department. Vol 1, Number 4, Journal of Validation Technology, August 1995, pp60-77

(16) Peine I.C., Quality Assurance Compliance, Procedures for Pharmaceutical and Biotechnology Manufacturers. Interpharm Press, IL, 1994

(17) The Gold Sheet, FDA's Inspection Concern for Bulk Pharmaceutical Chemical Firms, Quality Control Reports, The Gold Sheet, FDC Reports Inc., 1995

(18) U.S. Code of Federal Regulations, Current Good Manufacturing Practice for Finished Pharmaceuticals (Part 211), Food and Drug Administration, DHHS, 21 CFR CH.1, 4-1-95 Edition

(19) U.S. Code of Federal Regulations, Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; General (Part 210), Food and Drug Administration, DHHS, 21 CFR CH.1, 4-1-95 Edition

(20) USP. Microbiological Evaluation of Clean Rooms and Other Controlled Environments <1116>, In-Process Revision, Pharmacopoeial Forum, The United States Pharmacopoeial Convention, Inc., Volume 21, Number 2, March-April 1995

(21) WHO Expert Committee on Biological Standardization, Good Manufacturing Practices for Biological Products. Technical Report Series No. 822 Annex 1, WHO Geneva, 1992

(22) WHO Expert Committee on Biological Standardization. Guidelines for Performing One-Dilution Tests for Ensuring that Potencies of Diptheria and Tetanus Toxoid Containing Vaccines are Above the Minimum Required by WHO, WHO Geneva, BS/89.1618, 1989

(23) WHO Expert Committee on Biological Standardization. Potency Determination in Mice of Diptheria Toxoid in Vaccines by Serum Neutralization of Diptheria Toxin in Vero Cell Cultures, WHO Geneva, BS/89.1613 Rev. 1, 1990

(24) WHO Expert Committee on Biological Standardization. Requirements for Diphtheria, Tetanus, Pertussis and Combined Vaccines. Technical Report Series No. 800 Annex 2, WHO Geneva, 1990

(25) WHO Expert Committee on Biological Standardization. Requirements for Poliomyelitis Vaccine (oral). Technical Report Series, No. 800 Annex 1, WHO Geneva, 1990

(26) WHO Expert Committee on Biological Standardization. Requirements for Yellow Fever Vaccine (and Addendum 1987), Technical Report Series No. 594, Annex 1, 1975, and Technical Report Series No.771 Annex 9, 1988, WHO Geneva,

(27) WHO Expert Committee on Specifications for Pharmaceutical Preparations. Good Manufacturing Practices for Pharmaceutical Products. Technical Report Series No. 823 Annex 1, WHO Geneva, 1992

(28) WHO Laboratory Methods for the Testing for Potency of Diptheria (D), Tetanus (T), Pertussis (P) and Combined Vaccines, WHO, Geneva, Restricted Document, BLG/92.1

(29) WHO Laboratory Methods for the Titration of Live Virus Vaccines Using Cell Culture Techniques, For laboratories operating in support of the Expanded Programme on Immunization, Biologicals Unit, WHO, Geneva, Restricted Document, BLG/EPI/89.1

(30) WHO Manual of Laboratory Methods for Potency Testing of Vaccines used in the WHO Expanded Programme on Immunization. WHO/BLG/95.1

(31) WHO Production and Control of Tetanus Vaccine (Training Curriculum). WHO/VSQ/GEN/94.01- 94.11

(32) Whyte W., Donaldson N., How to Clean a Cleanroom. Microcontamination, November 1987

Added during review and editing:

(33) U.S. Current Manufacturing Practice: Proposed Amendment of Certain Requirements for Finished Pharmaceuticals, Food and Drug Administration, Federal Register, vol 61, No 87, May 1996.

(34) Loftus B.T., Nash R.A. Pharmaceutical Process Validation. Marcel Dekker Inc., 1984, p 227.

Appendix 4: Glossary

(Numbers in parentheses are the Reference numbers in Appendix 3. WHO definitions have been used when available.)

acceptance criteria: The product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units). (19)

action levels: Microbiological levels in the controlled environment, specified in the standard operating procedures, which when exceeded should trigger an investigation and a corrective action based on the investigation. (20)

air sampler: Devices or equipment used to sample a measured amount of air in a specified time to determine the particulate or microbiological status of air in the controlled environment. (20)

airborne particulate count (or total particulate count): Particles detected are 0.3 um, 0.5 um, and larger. When a number of particles is specified, it is the maximum allowable number of particles per cubic meter of air (or per cubic foot of air). (20)

airborne viable particulate count (or Total airborne aerobic microbial count): When a number of microorganisms is specified, it is the maximum number of colony-forming units (CFU) per cubic meter of air (or per cubic foot of air) that is associated with a Cleanliness Class of controlled environment based on the Airborne particulate count. (20)

airlock : An enclosed space with two or more doors, which is interposed between two or more rooms, e.g., of differing classes of cleanliness. for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods. (27)

alert levels : Microbial levels, specified in the standard operating procedures, which when exceeded should result in an investigation to ensure that the process is still within control. Alert levels are specific for a given facility and are established on the basis of baseline developed under an environmental monitoring program. These Alert levels can be modified depending on the trend analysis done in the monitoring program. Alert levels are always lower than Action levels. (20)

aseptic processing: A mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers/closures or packaging material for medical devices) and the transfer of the product into the container and its closure under microbiologic critically controlled conditions. (20)

audit: Inspection of facilities, functions, or records. (31)

authorized person: A person responsible for the release of batches of finished product for sale. In certain countries the batch documentation of a batch of finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release. (27)

batch (or lot): A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it could he expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. (27)

batch number (or lot number): A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc. (27)

batch numbering system: Standard operating procedure describing the details of the batch numbering. (27)

batch records: All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product. (27) (In reference 27, batch records for production are called “batch processing records” and for the packaging operations “batch packaging records”)

bioburden: Total number of microorganisms detected in or on an article prior to a sterilization treatment.(20)

biogenerator: A contained system, such as a fermentor, into which biological agents are introduced along with other materials so as to effect their multiplication or there production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal. (7) (also called a bioreactor)

biological agents: Microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not. (7)

bulk product: Any product that has completed all processing stages up to, but not including, final packaging. (27)

calibration: The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling- or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established. (27)

cell bank:

cell bank system: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank [fully characterized for identity and absence of contamination]. A number of containers from the master cell bank are sued to prepare a working cell bank. The cell bank system is validated for a passage level or

number of population doublings beyond that achieved during routine production.

master cell bank: A culture of [fully characterized] cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and sorted in such a manner as to ensure stability. A master cell bank is usually stored at -70 oC or lower.

working cell bank: A culture of cells derived from the master cell bank intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70 oC or lower. (7)

cell culture: The result from the in-vitro growth isolated from multicellular organisms. (7)

certification: Documented testimaony by qualified authorities that a system qualification, calibration, validation, or revalidation have been performed appropriately and the results are acceptable. (34)

clean area: An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction generation, and retention of contaminants within the area. (27)

clean room: A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate Cleanliness Class. In addition, the concentration of microorganisms in the environment is monitored; each Cleanliness Class defined is also assigned a microbiological level of air, surface, and personnel gear. (20)

clean/contained area: An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained areas at the same time. (7)

component: any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product. (19)

contained area: An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area. (7)

containment: The action of confining a biological agent or other entity within a defined space.

primary containment: A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

secondary containment: A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilizers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment. (7)

control: Controls resemble the unknown in composition and are assayed at the same time under the same test conditions by the same method. The results of these tests are used in calculating the mean and standard deviation of the test. Controls are used to measure accuracy. (4)

controlled environment: Any area in an aseptic process system for which airborne particulate and microorganism levels are controlled to specific levels, appropriate to the activities conducted within that environment. (20)

corrective action: Actions to be performed that are in standard operating procedures and that are triggered by exceeding Action levels. (20)

critical process: A process that may cause variation in the quality of the pharmaceutical product. (27)

cross-contamination: Contamination of a starting material. intermediate product, or finished product with another starting material or product during production. (27)

environmental isolates: Microorganisms that have been isolated from samples from the environmental monitoring program and that represent the microflora of an aseptic processing system. (20)

environmental monitoring program: Documented program, implemented through standard operating procedures, that describes in detail the procedures and methods used for monitoring particulates as well as microorganisms in controlled environments (air, surface, personnel gear). The program includes sampling sites, frequency of sampling, and investigative and corrective actions that must be followed if Alert or Action levels are exceeded. The methodology used for trend analysis is also described. (20)

finished product: A product that has undergone all stages of production, including packaging in its final container and labelling. (27)

in-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control. (27)

intermediate product: Partly processed material that must undergo further manufacturing steps before it becomes a bulk product. (27)

lot: (see terms listed under batch) (27)

manufacture: All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products, and the related controls. (27)

master formula: A document or set of documents specifying the starting materials with their quantities and the packaging, materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls. (27)

master record: A document or set of documents that serve as a basis for the batch documentation (blank batch record). (27)

material flow: The flow of material and personnel entering controlled environments should follow a specified and documented pathway that has been chosen to reduce or minimize the potential for microbial contamination of the product/closure/container systems. Deviation from the prescribed flow could result in increase in potential for microbial contamination. Material/personnel flow can changed, but the consequences of the changes from a microbiological

point of view should be assessed by responsible managers and must be authorized and documented. (20)

media growth promotion: Procedure that references Growth Promotion under Sterility Tests to demonstrate that media used in the microbiological environmental monitoring program, or in media-fill runs, are capable of supporting growth of indicator microorganisms and of environmental isolates from samples obtained through the monitoring program. (20)

packaging material: Any material including printed material employed in the packaging of a pharmaceutical product excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product. (27)

procedures: Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product. (7)

process: Set of interrelated resources and activities which transform inputs into outputs.(14)

processing instructions: See master formula. (27)

product contact areas: Areas and surfaces in a controlled environment that are in direct contact with either products, containers, or closures and the microbiological status of which can result in potential microbial contamination of the product/container/closure system. Once identified, these areas should be tested more frequently than non-product-contact areas or surfaces. (20)

production: All operations involved in the preparation of a pharmaceutical product from receipt of materials, through processing and packaging, to completion of the finished product. (27)

quality assurance: A wide ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. (27)

quality control: The part of GMP concerned with sampling, spccifications, and testing and with the organizations, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. (27)

quality management: All activities of the overall management function that determine the quality policy, objectives and responsibilities, and implement them by means such as quality planning, quality control, quality assurance and quality improvement within the quality system. (14)

quality policy: Overall intentions and direction of an organization with regard to quality, as formally expressed by top management. (14)

quality: Totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs. (14)

quarantine: The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing. (27)

reconciliation: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used. (27)

record: Provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product. (7)

reference standard: Any material of known identity and purity or potency. An official reference standard is one obtained from an official source such as BP, or USP, or WHO. A house reference standard may be obtained by thorough characterization for identity and purity or potency relative to an official reference standard, or by determination of absolute purity by other techniques. Depending on the intended use (qualitative or quantitative) and the nature of the assay, a greater or lesser degree of purity is acceptable. (4)

sampling plan: A documented plan that describes the procedures and methods for sampling of a controlled environment, identifies the sampling sites, the frequency and number of samples, that analysis of data, and the interpretation of results. (20)

sampling sites: Documented geographical location, within a controlled environment, where sampling for microbiological evaluation is taken. In general, sampling sites are selected because of their potential for product/container/closure contacts. (20)

seed lot

seed lot system: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

master seed lot: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below -70 oC. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

working seed lot: A culture of a micro-organism distributed from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots. (7)

specification: A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation. (27)

standard operating procedure (SOP): An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation. (27)

sterility: An acceptably high level of probability that a product processed in an aseptic system does not contain viable microorganisms. (20)

swabs: Devices provided that are used to sample irregular as well as regular surfaces for determination of microbial status. The swab, generally composed of a stick with an absorbent extremity, is moistened before sampling and used to sample a specified unit area of a surface. The swab is then rinsed in sterile saline or other suitable menstruum and the contents plated on nutrient agar plates to obtain an estimate of the viable microbial load on that surface. (20)

system: A regulated pattern of interacting activities and techniques that are united to form an organized whole. (27)

theoretical yield: The quantity that would be produced at any appropriate phase of manufacture, processing, or packaging of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production. (19)

Appendix 5: SOPs contributed by vaccine manufacturers

Massachusetts Public Health Biologic Laboratories

Biomanguinhos/FIOCRUZ, Brazil

Translation by Biomanguinhos

Gerencia General de Biologicos y Reactivos, Secretaria De Salud, Mexico

Originals Contributed by Mexico. Translation by GCL Bioconsult

(The above items were pasted in from original forms so are not available in electronic format.)

Appendix 6: Sample master formula for a hypothetical biological product

The following Master Formula is an example of the details, blanks and check boxes which are used to describe the manufacturing process and provide a form for recording and verifying the process as it is performed.

This Master Formula is not for a real production process - it is a hypothetical harvest which goes through several production steps to become a final bulk. It is assumed here that the bulk product is all made in one day. In a MF for an actual product, any batch that took more than one day to produce would have sections of the MF for each day giving the details of the preparation and the production process for each day.

(The following pages were pasted in from original forms so are not available in electronic format.)